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BCG-VACCINATION
IN CHILDREN
THE EFFECTIVITY AND SOME IMMUNE BIOLOGICAL MANIFESTATIONS

FROM THE OSLO MUNICIPAL HOME FOR INFANTS
(CHIEF: ALEX. BRINCHMANN, M.D.)

BCG-VACCINATION IN CHILDREN

THE EFFECTIVITY AND SOME IMMUNE BIOLOGICAL MANIFESTATIONS

BY

ROALD RINVIK

Acta Pædiatrica. Vol. XXXII. Supplementum I

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PART I.

Effectivity of BCG-vaccination.

I. Historical Review.

The question of immunisation against tuberculosis arose in connection with Robert Koch's discovery of the tubercle bacillus in 1882. From 1890 up to the present time a number of attempts have been made—mainly by means of animal experiments but also on humans—to find methods of immunisation, which afforded protection against this grave and widespread disease. The results of immunisation experiments with other infectious diseases, the demonstration of various antigens and antibodies in other bacterial infections pointed out the way also for the tubercle bacillus. The principle was based on the observation, that certain bacterial diseases render the organism relatively immune against further attacks of the same disease. An artificial, mild, and controllable *first* infection creates increased resistance to subsequent natural infection. This is the same principle as immunisation with cowpox; the process is therefore called vaccination.

The basis for tuberculosis vaccination is the so-called *Koch's phenomenon:* when a previously tuberculosis-infected guineapig is reinfected with tubercle bacilli by subcutaneous injection, this animal reacts entirely differently than a previously healthy guinea pig. In the course of 1 or 2 days there appears a strong inflammatory reaction with hemorrhagia and necrosis, but the superficial ulcer heals rapidly; the organism casts off the new focus, and general diffusion is prevented; the regional lymph glands do not become enlarged. In a previously healthy animal after the injection of tubercle bacilli a nodule developes after 8—14 days; an abscess is gradually formed which ulcerates 2—3 weeks after the injection. The ulceration

persists, the regional lymph glands swell as a sign of propagation of the infection, and the animal dies of general tuberculosis.

This changed manner of reaction for the previously infected animal is interpreted as an expression of the presence of an immunity in the animal's tissue as a result of the primary infection. This immunity sets into action mechanisms which localize and prevent the spreading of the superinfection.

From experience it is known that also in humans a tuberculosis infected individual attains increased resistance to new tuberculosis infections through previous infection. Children who have had tuberculosis can usually continue to live in a tuberculosis milieu without increased risk, but the acquired immunity is only relative.

The tremendous amount of work which has been done in the field of tuberculosis immunisation has followed 3 main lines, as either *live* or *killed* tubercle bacilli have been used, and in addition *bacteria extracts* of various kinds have been tested.

Aqueous *extracts* of the tubercle bacillus, lipoid soluble extracts and bacilli where the fat component has been removed have all been tried as anti-tuberculosis measures, in view of the possibility that the immunising principle might be isolated to the various albumins and lipoids in the bacillus. In this connection Koch's tuberculin therapy should also be mentioned. Positive results have been claimed for several of these extracts, but they have as yet not had any significant practical value. Experimental research in recent years however, seems to indicate that the immunising effect is localised to certain fragments of the bacilli, which can be extracted by special physico-chemical processes (*Widström*, 1941 inter al.).

Killed tubercle bacilli were tried as vaccine even by *Koch*, who found a certain immunity in guinea pigs after infection, but the local lesion was large. Other later investigations with heat-killed bacilli have been made by *Strauss and Trudeau*, *Calmette* (1907), and *Theobald Smith* (1908) among others; in some cases the bacilli were administered per os, in other cases by injection to various experimental animals, but the immunity attained was variable, of short duration and in many

cases doubtful. The first attempt at vaccinating humans with killed bacilli seems to have been made by *Maragliano* (Genua) in 1903. According to the method of smallpox vaccination he applied an emulsion of heat sterilised tubercle bacilli to a scratch on the arm. A number of individuals of all ages were inoculated in this manner, but nothing is mentioned of the results. In recent years several investigators, among them *Raw* in 1922, *Lange* in 1925 and *Petroff and Stuart* in 1926 have claimed good results with heat-killed bacilli. *Opie, Flahiff and Smith* (1939) confirm these results and claim to have achieved equally good results by vaccinating children with these heat-killed bacilli as with BCG. In addition to heat sterilisation, tubercle bacilli have been killed by numerous physico-chemical methods and tested as vaccine. However these experiments have not yielded any convincing results.

The first experiment with *live* tubercle bacilli seems to have been carried out as early as 1886 by *Cavagnis*. In subsequent years there were a number of other similar animal experiments, and in 1910 *Webb and Williams* were daring enough to inject 2 children of tuberculous parents, the one was 3 years, the other 3 months old. They administered small increasing doses of virulent bacilli, but the children remained anergic after these injections. Somewhat later *Webb and Gilbert* (1914) reported, that a third child which had been vaccinated, gave a positive tuberculin reaction afterwards. In 1925 *Selter* vaccinated 9 children with a virulent human strain of tubercle bacilli, which he mixed with bacillus protoplasm and called the vaccine vital tuberculin. All the vaccinated children became tuberculin positive and were later in good general condition. One child died of pneumonia 3 months after the inoculation, but with the exception of a small tuberculous nodule at the site of injection, no signs of tuberculosis were found post mortem even on inoculation of organ emulsions into guinea pigs.

However every vaccination with virulent tubercle bacilli must be regarded as hazardous. For this reason bacilli with reduced virulence or avirulent bacilli have been tested, and for this purpose heterologous strains of tubercle bacilli have been used. As early as 1889 *Mafucci* was able to differentiate between tuberculosis in birds and mammals, and *Theobald Smith*

(1898) demonstrated the differing qualities of human and bovine bacillus types. In moderate doses the bacilli of any one animal species are apathogenic for other animal species, and this principle forms the basis of the well-known animal vaccines Bovo- and Tauroman-vaccine, which were introduced by *von Behring and Römer* in 1903 and by *Koch and Schultz* in 1905 respectively for immunisation against cattle tuberculosis. This led to some immunity in the animals, but it was of short duration and was of no practical significance; several months after vaccination it was possible to demonstrate the employed human tubercle bacilli in the animals, and the bacilli were even excreted in their milk.

Friedman (1904) vaccinated humans, both prophylactically and therapeutically, with an emulsion of an acid resistant strain, where the virulence was reduced by animal passage through coldblooded animals. His method attracted great interest but its immunising effect proved to be small.

Arima, Aoyama and Ohnawa (1937) in Japan introduced the so-called A. O. vaccine for tuberculosis. They use a suspension of virulent tubercle bacilli which are made non-acid resistant by cultivation on a saponin-containing media.

Calmette's and *Guérin*'s experiments with BCG (Bacillus Calmette-Guérin) were based on a strain of tubercle bacilli from cattle. They had cultivated this strain for over 2 years on a special substratum which seemed to reduce the virulence of the bacillus. In 1908 they were able to report, that injection into cattle of live bacilli of this strain only caused a localized process without general tuberculosis. After continued cultivation on the same substratum the virulence of this strain was further reduced; the bacilli were harmless when injected into apes and rabbits and later even the most tuberculosis-sensitive animal, the guinea pig. In 1913 *Calmette* published his experiments on cattle, where the injection of these tubercle bacilli seemed to stimulate a considerable tuberculosis immunity. After subsequent superinfection the vaccinated animals showed no tuberculous organ lesions on post mortem examination. However when the lymph glands were crushed and injected into guinea pigs, a general tuberculosis resulted. *Calmette* took this as an indication that the acquired tuberculosis immunity was determined by live tubercle bacilli in the organism. In 1915 *Calmette* also demon-

strated the effectivity of the vaccine for contagious infection in cattle, and later he demonstrated that a subcutaneous injection of BCG gave a longer tuberculin allergy than the previously employed intravenous injections. All of these experiments of *Calmette* were made on animals, and all the experiments demonstrated that this tubercle bacillus was not dangerous, even though it was alive. No progressive tuberculosis was demonstrated. *Calmette* believed that his bacillus culture had become a "virus fixe", i. e. a virus which neither in the vaccinated organism nor transferred to other organisms regains its original virulence. Later bacteriological investigations however, have not quite agreed in confirming this. Several investigators have demonstrated a variation in its virulence.

The BCG-vaccine does not seem to have attained any practical application in veterinary medecine. It is in the preventive fight against human tuberculosis that BCG gradually stimulates the greatest expectations and leads to one of the most extensive and lively discussions in medical circles in the past decennia. In 1921 *Weill-Hallé* made the first experiment on humans with BCG on infants. *Calmette* believed that the bearer of a benign tuberculous infection, obtained by the injection of the avirulent BCG — an infection which does not result in tuberculous disease — had a pronounced resistance to new infections. Therefore children should be impregnated with these live, avirulent tubercle bacilli as early as possible.

It had previously been shown in animal experiments (*Behring*, *Calmette*, *Guérin* inter al.) that the tubercle bacillus could diffuse through the membranes of the alimentary canal to the mesenterial glands. From there they spread further throughout the organism. *Behring* (and *Calmette*) believed that this was the most common manner of infection for human tuberculosis also. This resorbtion takes place more readily in young animals than in old ones, and this gave rise to the per oral dosage of the vaccine which was preferably employed in the early days of its application. Newborn children were given 3 oral doses of 2 mg. at intervals of a few days, and up to the beginning of 1924 *Weill-Hallé* had vaccinated 850 infants in this manner. In the same year, however, he had also begun to employ *subcutaneous* vaccination, as the per oral method

did not give constant results on tuberculin testing. The first statistical results published showed a striking effect of the BCG-vaccine and awakened, especially in France, violent agitation for its extensive application in prophylactic work with tuberculosis in children. A critical perusal of the statistical data revealed, however, that the conclusions drawn from the material presented were quite indefensible, and the controls were poor. A violent opposition was aroused, not only in other European countries but also within French medical circles. The lively discussion led to a critical test of the method both in other European contries and on other continents. In Scandinavia *Wallgren*'s name is particularly connected to the BCG-question in children, first through his critical appraisal of Calmette's results, and later through the introduction of the *intracutaneous* method of vaccination in 1928. *Wallgren* also points out the importance of isolation of the vaccinated until the immunity has manifested itself by a positive tuberculin reaction. On these principles he has BCG-vaccinated practically all of the children who are born in a tuberculous milieu in Gothenburg and has achieved statistically great results.

In Norway *Scheel* and *Heimbeck* have published some of the most important results in recent years on the immunising effect of BCG-vaccine. These investigations are concerned chiefly with adults who are particularly exposed to tuberculous infection (medical students and student nurses). Scandinavia has also made valuable contributions to the field of experimental BCG-research (*Jensen*, *Bindslev* and *Holm* from Denmark, *Widström*, Sweden, and not least *Birkhaug*, who has done remarkable work in this field with animal experiments from the BCG-laboratory in Bergen).

From America among others *Park* and the Hungarian *C. Kereszturi* have published very accurately observed material, and emphasize especially all the reservations which must be made in a comparison of vaccinated and non-vaccinated in evaluating the effectivity of vaccination.

In 1938 *Rosenthal* (America) published a new vaccination method: 30—40 superficial skin pricks are made through a drop of BCG-vaccine on the skin, through which the vaccine is absorbed. *Weill-Hallé* reported a modification of this *per-*

cutaneous method in 1939, with a cross scratch in the skin through a drop of BCG-vaccine. These percutaneous methods yield more rapid and more lasting allergy both in animal experiments and in humans.

As early as 1930 *Chaussinand* tried intramuscular dosage of BCG-vaccine but found no advantage with this method in comparison to intra- and subcutaneous application. However the allergy seemed to develop more rapidly.

The discussion of BCG has continued to the present with reports from almost all parts of the world. The innumerable publications indicate the considerable significance of the question in medical circles, and the number of individuals vaccinated is rising rapidly everywhere. In France for example, the number of vaccinated children is more than 1½ million. In Norway over 6000 vaccinations were made in 1942.

II. Complications and Subsidiary Effects in Connection with BCG-vaccination.

The most important condition for the application of a vaccine to humans is that it is not harmful to the organism. The numerous animal experiments with BCG have never shown progressive tuberculous organ injuries in animals. However the vaccination produced localised tuberculous lesions with the usual histological picture of tubercles.

Chaussinand and Tempé reported an experiment in 1930 where a 7 months old hydrocephalus patient was given 2 mg. BCG intraperitoneally. On post mortem examination 13 months later small tubercles were found in the liver, kidneys and spleen without caseation. Inoculation in guinea pigs gave negative results. In spite of the enormous dose employed and the intraperitoneal application, there was no increase of virulence.

However a number of vaccinations have been reported which have resulted in death, where the vaccination has been blamed. The best known of these is the Lübeck catastrophe in 1930 where 75 children of 249 who had been given BCG perorally, died of tuberculosis some months later. It was discovered that the vaccine had been contaminated with a virulent strain of human tubercle bacilli, which was stored in

the same incubator as the BCG-culture. Other cases of death after BCG are also reported, but there is no proof in a single case that BCG has been the cause of death, although some laboratory investigators (*Petroff* inter al.) have shown that the BCG strain may dissociate in a virulent (minimal) fraction under certain conditions. *B. Epstein* (1935) reported 5 perorally vaccinated and 4 subcutaneously injected children who were examined post mortem. The examination revealed no traces of tuberculosis in any of the cases in spite of careful examination of series sections, animal inoculations and cultivation tests.

Kereszturi and Park (1936) conclude on the basis of investigations over a pericd of 8 years of 175 non-exposed children and 515 who were exposed to tuberculous infection, that BCG never has a harmful effect. In all of those who died of tuberculosis it was possible to demonstrate human tubercle bacilli. Of the non-exposed, 9 of 15 dead came to post mortem examination, and no tuberculous lesions could be demonstrated. From one patient, perorally vaccinated, who died of alimentary intoxication, BCG was cultivated from mesenterial glands; on inoculation in guinea pigs and rabbits however, there were no tuberculous lesions.

It has frequently been reported that BCG can be cultivated from the abscess which appears locally after the injection, even many months later; however cultivation and animal experiments reveal no increase in virulence.

Some clinical reaction symptoms have been reported in connection with the vaccination such as temporary rise in temperature, changes in blood sedimentation and other blood changes as well as a disposition to catarrhal affections. As the result of a careful clinical observation of 37 vaccinated children *Epstein* (1935) claims that there are no clinical indications of general reaction after vaccination. However in some cases he has found roentgenological changes of the bronchial glands, after both peroral and subcutaneous dosage. These changes receded rapidly and may just as well be due to other causes than BCG; with our present knowledge transitory unspecific roentgenological lung and hilus changes are not rare and are particularly common in childhood.

A *local reaction* in the form of the cold abscess which dev-

elopes gradually from the infiltration after the injection is however rather constant. The abscess may be large and sometimes rather bothersome due to the persisting secretion. Cosmetically the resulting scar may also be undesirable. In some cases there may be swelling of the regional lymph glands, sometimes with the development of abscesses and subsequent discomforts.

Our material has not been observed with particular emphasis on the immediate clinical reaction to BCG-vaccine. Most of the individuals vaccinated have, however, been under daily control for several months afterwards (daily temperature measuring among other things), and the records and temperature curves reveal no indications of symptoms which might be related to the vaccination. In some few cases there has been swelling of the regional lymph glands, but these have never abscessed.

As a conclusion to the numerous investigations which have been made on the risk of BCG-vaccination for humans, it may be said that not a single case of the vaccinated millions has shown any harmful effect of a properly produced and handled vaccine.

III. Effectivity of the Vaccination.

A. Other investigations.

The statistical data of *Calmette*'s first publication in 1927 on the immunising effect of BCG showed a mortality for the vaccinated of 0.8 % as against 26 % for the non-vaccinated among children from 1 to 2 years of age, who lived in an open tuberculous milieu. This remarkable result led to a widespread and violent criticism which demonstrated a number of inaccuracies and omissions in the figures presented, and showed that the results reported were unreliable. Among other errors *Calmette* employed ordinary child mortality as comparison and thus demonstrated statistically a paraspecific effect on the BCG vaccinated children, which placed them in a more favorable position also in relation to other diseases than tuberculosis. In consideration of the fact that tuberculosis — even in a strongly infected milieu — is responsible for only *some* of the actual deaths, and that debile and premature children usually were

not vaccinated, it is obvious how misleading such a comparison can be.

But even though the criticism was devastating and the discussion violent, interest was aroused for a critical test of the vaccine.

A number of investigations on the effectivity of the vaccine have since been published, but their methods of evaluation have been diversified. Some compare the tuberculosis mortality in the entire population with the vaccinated group, others use children of different age as controls etc.

It is therefore practical to select from among the many publications those where the material seems to be most reliably investigated, and where the material is relatively comparable with the material in the present investigation.

Since 1927 *Arvid Wallgren* has applied BCG-vaccine in Gothenburg and has published his material up to $^1/_1$ 1934. 353 children from an infected milieu had been vaccinated up to that time, and of these 230 were exposed. 172 of these were under 1 year. The material was carefully examined and controls were made at least once a year, also roentgenologically. 2 children had died but not of tuberculosis (verified by post mortem examinations). In one child (1 year old with 6 months exposure) definite hilus changes were demonstrated roentgenologically in connection with an illness of short duration, where the tuberculous process was remarkably benign. In addition there were slight or suspect hilus changes in 11, while the rest, 216 patients, showed completely normal roentgenological findings.

Wallgren insists on sufficient isolation both before and after vaccination (in all *at least* 3—4 months) and admits the overwhelming significance of this factor, inter alia that an eventual risk of infection is delayed until almost one year of age.

Anderson and Belfrage have continued BCG-vaccination in Gothenburg according to *Wallgren*'s principles, and they published their results in 1939.

By the end of 1937 the total number vaccinated had reached *1069*, and of these 905 had been re-examined. All were healthy when examined. Of 379 exposed cases the authors state

that none had tuberculosis. The roentgen-examined showed "in many cases the presence of minute, very dense, occasionally calcareous spots in the hili, but no signs of progressive or healed tuberculous processes in either the hili or the parenchyma were found in a single case." However these conclusions go too far. Roentgenological calcareous spots, even though small, in the hilus or lungs are in the large majority of cases due to earlier tuberculous processes; to neglect these as "no signs of healed tuberculosis" is hardly allowable, especially when they have been found "in many cases". It is much more probable that these are indications of slight undergone tuberculous infections.

In this material 15 are dead, but no indication of tuberculous disease was found in any of them (9 pcst mortem examinations).

As practically all of the tuberculosis-threatened children in Gothenburg are vaccinated, there is no comparable control material. But with this consequent application of vaccination, the effect should be detectable in the total tuberculosis mortality statistics in Gothenburg, and this proves to be the case. In the two 5 year pericds *before* the intrcduction of vaccination in 1927 the tuberculosis mortality for small children was about 4 ‰. In the two 5 year pericds *after* vaccination it had sunk to 1.4 ‰ and 0.5 ‰ respectively. The mortality curve for adults (not vaccinated) showed a comparatively insignificant decrease.

From America *Park* and the Hungarian *G. Kereszturi* have published a number of reports on BCG- vaccination in children. They have followed their material carefully since 1927· and they have made great efforts to find the most comparable groups of non-vaccinated children as controls. The bases of their evaluations are thus as ideal as possible, as the entire material is carefully controlled and analysed. After 8 years' studies they publish their final report in 1936, which shows a tuberculosis mortality for the vaccinated children of 0.9 % (of 690) as against 2.7 % for 755 controls. A statistical calculation of children exposed to infection from a *destructive* tuberculous milieu shows a mortality of 0.9 % among 459 vaccinated, while the mortality among 525 controls goes up to 3.2 %. No information is given as to the morbidity.

Winge (1942) has published extensive BCG-material from Denmark including a large number of children; similarly have *Dahl, Hertzberg and Refsum* in their preliminary report from The Bureau of Public Health in Oslo in 1940 included 637 children from 0—14 years of age. However both these publications lack control material, but both conclude that the vaccination has an advantageous effect. Part of the material from the Oslo Bureau of Public Health is included in the material to be described below.

Although they fall somewhat outside the field of the present investigation *Scheel*'s (1935) and *Heimbeck*'s (1936) results with BCG-vaccination should be mentioned. Their material consists only of adults, but is one of the fundamental investigations which clearly demonstrate the immunising effect of the vaccine. Both *Scheel*'s material of medical students and *Heimbeck*'s of student nurses show a higher tuberculosis morbidity in the tuberculin negative than in the tuberculin positive. Among *Scheel*'s students the tuberculosis morbidity falls to 1.87 % after vaccination, while it is 4.78 % for the non-vaccinated tuberculin negative. *Heimbeck*'s student nurses had 2.8 % tuberculosis morbidity after vaccination and positive tuberculin reaction as compared to 34.3 % for the non-vacinated. The mortality figures for his material were 0.4 % and 3.6 % respectively.

B. Plan of work.

This investigation aims to elucidate whether BCG-vaccination has any effect on tuberculosis *morbidity*. Are children in a tuberculous milieu less subject to infection if they are BCG-vaccinated? Are the tuberculous infections these children may eventually acquire less severe than in the non-vaccinated?

The question of tuberculosis *mortality* in the respective groups vaccinated and non-vaccinated follows logically after the first.

A retrospective examination of a material observed over a longer period might also possibly reveal clinical information as to the question of the *duration* of an eventual vaccination effectivity.

One of the difficulties in determining the actual effectivity of BCG, especially in children where age at the time of exposure plays such an important part, consists in finding a homologous control material. *Levine, Vogel* and *Rosenberg* (1938) emphasize this point particularly, and mention a number of factors which should be equal within the 2 groups to be compared. Most important is the intensity of the exposure (the bacillary frequency, massivity and also virulence) and the exposure age. It is well known that a tuberculosis exposure during the first year of life gives a much poorer prognosis than later. Further: milieu factors with differing social standards of living. An important factor here is the cooperation and intelligence of the parents, and the consequent significance of prophylactic measures. This factor is clearly illustrated in *H. v. den Berg*'s (1929) publications. In children under 3 months, where the infection-bearing environment was prohylactically instructed, the mortality was 3.8 %, while the mortality in children in similar families which had no prophylactic instruction went up to 35.7 %.

Both vaccinated and controls must be followed up and examined in the same manner, and eventual isolation should be carried out for both categories.

To fulfill all these demands simultaneously is hardly practicable, unless the children in both groups are treated in the same manner from birth. How difficult a *practical* realization of these optimum demands may be, is shown by the work of *Park and Kereszturi*. In a large material where they tried to compare vaccinated and control children under identical conditions, it was found that of 206 infants, only 3 pairs were comparable.

C. Personal investgations.

1. Material.

The material consists only of children from a tuberculosis-threatened milieu, where one or more members of the family have been reported for tuberculous disease. They are all born between 1926—1940, and are mostly from working class homes, some also from middle class families in Oslo and its surroundings.

A large number of the children have stayed at the Infant's Home in Åkebergveien for a shorter or longer period. This is a home for tuberculosis-threatened children founded in 1922. Since 1926 BCG-vaccination has been practiced here. Before 1930 the children were treated en bloc without isolation of possibly infected children. Up to that time there has thus been a certain, although minimum, possibility for contact infection of the previously uninfected children within the Home. However we are aware of no cases of acquired tuberculosis during this period. Since 1930 the tuberculosis infected and also tuberculosis sick children have been isolated in a separate section without any contact with the other inmates. Contagious infection from the outside can be disregarded, as the parents are not allowed to have any contact with the children as long as they are at the institution. Control examinations are made of the entire personnel, so that the non-infected children are in an absolutely tuberculosis-free milieu as long as they are institutionalized.

As a rule the infants are brought to the Home immediately after birth, but the duration of their stay there varies, from a few months up to 3—4 years. They are then either sent home or are placed in foster homes or Childrens Homes, eventually for adoption.

The children who have been at the Infants Home have thus all, both vaccinated and controls, had the advantage of isolation from a tuberculous milieu during the first part of their lives.

The Home also controls its patients to a large extent after they have left, so that there is good opportunity of following the children in their development, their health, danger of infection in the home and family etc.

The rest of the material is collected from the tuberculosis records of Oslo's Bureau of Public Health. This institution holds control over the majority of the tuberculosis patients reported in Oslo, and the records here form the basis of this part of the material. When a child is born in a family where tuberculosis has been reported, a special "infant envelope" is made up for the child where detailed records of its health are kept from birth. The same is done for children who come under control later.

For both the material from the Infant's Home and that from the Bureau of Public Health there is the advantage of comparatively constant and homogenous control examinations.

The distribution of the material appears from the following:

Year of birth	Non-vaccinated		BCG-vaccinated	
	Home	B. P. H.	Home	B. P. H.
1926—30	36	194	61	29
1931—35	43	83	52	24
1936—40	17	27	88	39
Total	96	304	201	92
	400		293	

Vaccinated.

The total number vaccinated is *293*. Of these 15 were vaccinated perorally but are not treated separately in the investigation, as most of them were afterwards vaccinated parenterally. A few of the others are vaccinated subcutaneously, but the majority intracutaneously with vaccine doses varying from 0.02 to 0.10 mg. BCG. Percutaneous vaccination has not been employed.

The majority of these, 201, are vaccinated at the Infant's Home, and *Wallgren*'s principles have been followed as far as possible, even though all of his demands could not be fullfilled in detail. Naturally none have been vaccinated without first showing sufficient negative tuberculin tests (Mantoux), and for most of the children the period of isolation before vaccination has been so long, that vaccination during the incubation period of an eventual virulent infection can probably be excluded. The large majority have also been isolated sufficiently after the vaccination, i. e. until positive tuberculin reactions can be demonstrated, eventually after revaccination.

Where it has not been possible to observe the optimum conditions for vaccination, the parents have been instructed

as to the danger of infection etc., or the child has been removed from eventual sources of infection during the time immediately after vaccination.

These children have mostly been vaccinated between the ages of 0 and 3 years, and there has generally been no risk of infection until after they are discharged. During their stay at the Home this group of vaccinated children comprises an ideal material for investigation of the biological circumstances attendant on the vaccination, since these children are in an absolutely tuberculosis-free milieu.

92 children were vaccinated *outside* the Infant's Home, usually at the Bureau of Public Health, some by private physicians and some at maternity hospitals.

Most of the children in this group are vaccinated later in childhood, often after they have begun to attend school. These children have as a rule not been isolated either before or after vaccination. There is thus a possibility for vaccination in the pre-allergic phase of a virulent infection or a risk of infection before the vaccination allergy is attained. However the majority were roentgenologically examined beforehand by fluoroscoping (Oslo Bureau of Public Health), and all had negative tuberculin reactions (usually Pirquet).

The new born in this material are treated in the same manner as those in the Infant's Home material, as these children are usually admitted to the Home after vaccination. The figures below show that over half of the vaccinations have been performed during the first year of life.

Age when vaccinated-			
0— 3 months	61	155	
3— 6 »	29		
6—12	65		
1— 2 years	45		
2— 3 »	28		
3— 5 »	28		
5—10 »	29		
> 10 »	8		
	293		

Control material.

Among the non-vaccinated children, 96 have stayed at the Infant's Home for a shorter or longer period- while *304* have not had the advantage of this isolation. Otherwise the same conditions hold for the respective groups here as mentioned above for the two categories of the vaccinated children.

For both the vaccinated and the non-vaccinated there is thus a comparatively equal social standard and probably a comparatively similar infection milieu: in addition to the ordinary chances of infection they have all been exposed to the risk of infection from tuberculous members of their families in varying degrees. The risk of infection will naturally vary considerably. The contact *possibilities* are here the most important. For example the source of infection may, at the time of the child's birth and during its early life, have been under treatment outside the home (sanatorium etc.), or the child may have been brought to the Infant's Home immediately after birth and thus have completely avoided contact during the first important months.

Further the *state of health* of the source of infection is of great significance in evaluating the effectivity of the vaccination, as a destructive form of tuberculosis in the child's immediate surroundings will expose it to a much greater infection risk than a non-destructive form.

These particular conditions have been taken into consideration in the *follow-up examinations.*

These are made partly from the records of the Oslo Bureau of Public Health, partly from the records of the Infant's Home. For each individual case, both for the vaccinated children and the control group, information as to the sources of infection has been obtained: the time of their contact with the child, their health condition, the child's eventual isolation from the source of infection etc. Through the same records it has also been attempted to follow the children through the control examinations made (general examinations, tuberculin tests, roentgen examinations). As mentioned above the Oslo Bureau of Public Health has records of practically all the cases of

tuberculosis in Oslo and its environs, so that they also have records of the children who have stayed at the Infant's Home, even though the Home may have lost track of the child. Supplementary information has also been obtained from examinations by school physicians and from private physicians, from health records etc. in cases where the child may have moved away from Oslo.

Practically all of the children who have stayed at the Infant's Home are *personally* re-examined, and this holds especially for the vaccinated children. The examination has consisted in a general physical examination and tuberculin tests (Mantoux); in most of the cases roentgenological examinations have also been made, and where their interpretation has been doubtful they have been submitted to the Roentgen Department of the State Hospital for objective evaluation.

2. *The tuberculin reaction after vaccination.*

a. Methods.

For the vaccinations which have been controlled outside the Infant's Home, Pirquet's tests with scratches have usually been employed, and an infiltration of at least 2 mm. after 2 days has been accepted as sufficient for a positive result in accordance with the rules of the Bureau of Public Health. Both Hamburger's salve test and Pirquet have been used on the children at the Infant's Home. When these have given a pronounced reaction, that is marked small-papular rubor after 3 days, or a Pirquet with infiltration *over* 4—5 mm. after at least 2 days, this has been regarded as sufficient for a positive test. When they have not reacted, Mantoux' reaction has been employed, previously with doses of ½ mg., during the last 8 years with 1 mg. as standard dose. A Mantoux reaction is regarded as positive when there is a measurable rubor *and* infiltration of 10 × 10 mm. measured as surface area in 2 perpendicular directions after 3 days. Ordinary Old-tuberculin is used in all the tests.

The results of all the intracutaneous tuberculin tests are dependant on the fact that the tuberculin is actually applied intracutaneously; if it goes deeper the tuberculin will diffuse

rapidly, and the reactions will be weak or negative. No guarantee for completely accurate technique in this respect can be given. But the injections are made by experienced physicians and all the readings have always been controlled by the same chief. We have a compensation for eventual sporadic failure of the technique in individual reactions in the high frequency with which the tuberculin tests are made, — in some children up to 50—60 times during their stay at the Infant's Home.

b. Frequency of positive tuberculin reactions.

The result appears from the following figures:

Tuberculin reactions after vacc. I.

Year	Pos.	Neg.	Unknown	% pos.
1926—30[1]	55	29	6	65.4
1931—35[2]	54	20	2	72.9
1936—40.....	93	16	18	85.3
	202	65	26	75.6
		293		

[1] 14 vaccinated perorally: among these 6 pos., 7 neg., 1 unknown.
[2] 1 peroral vaccination neg.

This accounts for all of the children with positive reactions after the first vaccination, judged partly by the standards of the Bureau of Public Health, partly by those of the Infant's Home, in all *75.6* %. No consideration is taken here of the isolation problem either before or after vaccination—some patients were isolated, others not. Thus for the non-isolated the tuberculin allergy may possibly be due to a virulent infection. Nevertheless this maximum figure for tuberculin positive is not higher than 75.6 %. The percentage will rise a little in consideration of the fact, that 15 were vaccinated perorally (of these 8 negative), and the number with unknown tuberculin allergy is also relatively large. The rising percent of positively reacting children in the 2 last 5 year periods is probably an indication, that the vaccine employed has been progressively more effective.

A compilation of the positive reactions in relation to

the age of the children at the time of vaccination shows relatively similar distribution. It is in any case not demonstrated that it is more difficult to make children under 1 year allergic than older children.

Age when vaccinated	n	Pos.	Neg,	Un known	% Pos.
0— 1 year	155 (9 oral)	104	38	13	73.2
1— 2 years	45 (4 »)	34	8	3	80.9
2— 3 »	28 (1 »)	17	6	5	73.9
3— 5 »	28	21	6	1	77.7
5—10 »	29 (1 »)	19	7	3	73.0
> 10 »	8	7		1	
	293	202	65	26	75.6

The time of the determination of positive or negative reaction is not definitely fixed — it varies between 3 and 6 months after vaccination — as re-vaccination is usually performed at the Infant's Home if the tuberculin reactions are not positive in the course of the first 3—4 months.

The figures presented here are considerably lower than those of other authors. Most publications report positive tuberculin reactions in about 90—95 % after injection vaccination. (*Dahl*, *Hertzberg*, *Refsum* 95—98 %, *Wallgren* ca. 90 %, *Anderson* 97 %, *Winge* 90—93 %, *Scheel* 70 % and *Heimbeck* 72 %). With *Rosenthal*'s percutaneous method *Birkhaug* reports 98.4 % tuberculin allergy with Mantoux after 8 weeks.

The cause of this deviation in our material probably lies for the most part in the fact that most of it has been isolated in the Infant's Home for a shorter or longer period after vaccination. The effect of eventual contact infection is eliminated, and the figure thus gives a more accurate expression of tuberculin allergy after a pure BCG infection without any mixture.

However this hardly explains the entire difference between the figures found in this material and those reported by other investigators. *Wallgren*'s material for example also consists of children with practically the same isolation conditions, and yet he finds about 90 % allergy.

Wallgren always employs Mantoux' reaction (1 mg.) for his tuberculin tests, and this provides some explanation; with intracutaneous tuberculin tests the allergy will manifest itself more readily after vaccination than with percutaneous Pirquet tests (*Brinchmann* inter al.).

An insignificant number of our children are vaccinated subcutaneously, but the number is so small that it can hardly influence the results.

c. Time of appearance of the tuberculin allergy.

When the *time* of appearance of the tuberculin allergy is to be determined, it is necessary to isolate the patients for a sufficient length of time both before and after vaccination in order to eliminate the influence of an eventual virulent component. This is however difficult to carry out in practice. Even in our material which includes so many isolated children, less than $^1/_3$ can supply reliable information as to the pre-allergic period after the first vaccination. Among 84 children (0—3 years of age) the allergy manifested itself most frequently between 40—80 days after vaccination, which appears from the following table:

The pre-allergic period.

Manifestation of pos. tuberculin reaction n days after vacc. I.

Days	30	30—40	40—60	60—80	80—100	> 100
Dosage:						
Oral	1	1	1	1		1
0.03 mg.				1		
0.05 »	7	1	10	6	5	2
0.075 »				1		
0.10 »	2	8	10	9	7	7
0.20 »					3	
	10	10	21	18	15	10=84

The same dose of the same vaccine may in one child give tuberculin allergy after 4 weeks, in another child not until after 8—10—12 weeks.

The vaccine dosage does not seem to be of particular significance. In 4 other children aged 5 months, 9 months, 11 months and $2^{4}/_{12}$ years (not included in the main body of the material), who were by mistake given 1 mg. BCG intracutaneously in 1941 (vaccine from a bottle for Rosenthal's percutaneous vaccination was employed), the allergy did not appear until 44, 56 and 56 days, in the 4th not until after 153 days (ambulant control). However in a statistical compilation of 68 children *Wallgren* (1934) claims, that large doses give more rapid tuberculin allergy. In a single case there was in our material allergy after 16 days, dose 0.05 (doubtful reaction), in one case after 19 days with dose 0.10, and one child showed allergy 3 weeks after vaccination (dose 0.10). This short pre-allergic phase is exceptional after initial vaccination, — all the others are longer than 4 weeks.

Eight children who, experimenti causae, were given 2 vaccination doses at 7—17 days interval showed more rapid sensitization than usual, as the allergy in 3 of them appeared 18, 18 and 19 days after vaccination I (cf. Part II, Table 3). The longest controlled period before the manifestation of tuberculin allergy was 7 months (dose 0.10).

There seems to be no parallelism between the intensity of the local BCG reaction and the tuberculin reaction. There is however a certain relation, as only once have we observed a positive tuberculin reaction where the local reaction at the site of BCG-injection was completely negative. Cf. Table I, Part II, pat. 29/33. Positive local reactions are not infrequently seen even though the tuberculin reaction may be negative.

d) Duration of the tuberculin allergy.

It is even more difficult to answer the much discussed question of the *duration of the allergy after vaccination.* This is of considerable practical significance, especially in order to determine the time of eventual revaccination. The absolutely necessary isolation required in order to determine this interval meets with the greatest practical difficulties. For example the parents may insist on taking the child home, or a chance hospitalization may bring the child in contact, which may

immediately eliminate the requirements of an absolutely tuberculosis-free milieu. Moreover frequent tuberculin tests must be made; intracutaneous reactions are necessary as the allergy then manifests itself much longer than when cutaneous tests are employed *(Brinchmann)*. The tuberculin allergy after BCG-vaccination also has certain characteristics which must be taken into consideration. In the material from the Infant's Home the tuberculin tests are made with unusual frequency and at short intervals for the individual patients (up to 50—60 times for some during their stay). A study of these tuberculin tests will immediately reveal the variations in the reactions of the individual children: they may be slight positive, then again strong positive, and so completely negative for a time, then *again positive* to varying degrees. Mantoux' reaction for example may show rubor but no infiltration; often it may be definitely positive after 2 days, but after 72 hours it may have disappeared again. There seems to be a threshold which is not always reached, — the tuberculin sensitivity seems to waver around this threshold, sometimes over, when it is expressed by a positive reaction, and sometimes under. These slighter, weaker tuberculin reactions after BCG are well known, and have given rise to such expressions as "small Pirquets", "vaccine Pirquets" etc. But it is just this condition which makes it so difficult to determine both the time of appearance of the tuberculin allergy and especially its duration, even when the children are kept in a tuberculosis-free milieu. If the duration is calculated from the first positive Mantoux to the first negative, this should perhaps be on the safe side, but as mentioned above a negative reaction may again become positive even though only for a shorter time.

From animal experiments we know that tuberculin allergy after BCG-vaccination lasts for 6—9 months, up to 1 year.

In 1934 *Brinchmann* published 15 cases from this material, and in only 2 did the allergy last as long as 2 years. If we look through the material today and exclude all cases where the slightest doubt of contact infection may be present (sufficient isolation), we find only 30 initially vaccinated children with a duration of the tuberculin reaction more than 6 months after

vaccination. These have an absolutely "pure" BCG-allergy, i. e. an allergy where all virulent infection can be excluded. Calculated from the first positive to the first negative Mantoux (which is followed by constantly negative reactions) the following figures are obtained, representing the *maximum* duration for these patients:

Duration of the allergy.

Months	6—9	9—12	12—18	18—24	24—30	⩾ 30
n children	8	12	3	4	2	1

The duration of the allergy thus seems to center around 9—12 months. The longest controlled duration of the allergy is $2^{8}/_{12}$ years. This agrees with *Brinchmann*'s earlier results, according to which he recommends revaccination after about 1 year. To begin with *Wallgren* also claimed a probable allergy duration of 1 year but extended it to 10 years after *Anderson'—Belfrages* publication in 1939. Control examinations of the Gothenburg material showed a high percent of tuberculin positive for all those vaccinated with BCG up to 10 years after vaccination (96—97 %). When these vaccinated children were grouped according to certain, uncertain and no exposure, the percent of tuberculin positive was practically the same for all 3 groups, from which *Anderson* and *Belfrage* conclude that the non-exposed positive reactions are due to the BCG-vaccination, and thus assume a duration of up to 10 years for BCG-tuberculin allergy. However it is very difficult in their material to exclude the possibilities of infection where only children from an infected milieu have been vaccinated,—the allergy must to a great extent be confused with infection allergy, especially in consideration of the many patients where control examination revealed positive roentgen findings (calcifications). Later *Anderson* (1942) reduces his approximation of the duration of the tuberculin allergy to 5 years.

Park and Kereszturi's publications (1933) claim an allergy duration of between 2—3 years.

Revaccination does not seem to give longer duration of tuberculin allergy than the intial vaccination. This is apparent

from the fact, among others, that among 89 revaccinated in this material, 34 are revaccinated more than once. *Brinchmann* has previously demonstrated, that judging by positive Pirquet 13 of 24 revaccinated had an average allergy duration of maximum 6 months, by Mantoux 9 months.

The same inconstant and varying tuberculin reactions are also seen after revaccination. We have frequently vaccinated 5—6, even 7 times without achieving a reliable tuberculin allergy.

It is clear that *individual variations* play an important part for the manifestation of tuberculin allergy after BCG-vaccination, its frequency, time of appearance and duration of the allergy. It seems that some children become allergic much more readily than others, some show stronger tuberculin reactions and retain their allergy for a longer time than others, but it has not been possible to demonstrate any particular reason for these individual deviations. The explanation probably lies in differences in allergic capacity from individual to individual. This is probably particularly true of children. *Freund* (1931) has shown that in young, infected guinea pigs (under 1 month), the skin allergy may fail to manifest itself while the "internal" allergy is present and demonstrable. The animals showed a negative tuberculin reaction in the skin, but died of tuberculin shock when the tuberculin was injected intraperitoneally. *Freund* believes this is due to anatomical and physiological differences in the skin of young and old animals. In consideration of the large deviations shown by the normal variation of other physiological functions in children (e. g. growth), it is possible that the same is true of the allergic disposition; this may also be regarded as a normal physiological reaction.

In spite of the large number of tuberculin tests made we have *never* seen inflammation of the BCG-infiltrations or scars in connection with the tuberculin injections. *Dahl, Hertzberg and Refsum* (1941) report a focal reaction of this type after a Pirquet reaction which seems to be a completely isolated phenomenon. This is not confirmed anywhere in the literature, and it was not possible to produce this focal reaction by special experiments where the tuberculin was injected between remains of

earlier BCG-vaccinations. (In a personal communication *F. Marstrander* (1943) has demonstrated focal reaction in the BCG scar of an adult after 1 mg. O. T.)

3. Statistical results.

a. Material.

As mentioned in the above description of the material, all the children are from a tuberculous milieu, i. e. at least one family member has been reported for tuberculosis in one form or another.

This does not necessarily mean that the child has *been in contact* with the infection. For example the source of infection may be removed from the child before birth, and for such a long time that the risk of infection is delayed from the important first year of life until the end of that time or even later. The same conditions prevail if the child has been placed in the Infant's Home as soon as the possibility of infection has been discovered, and remains there for several years. The children thus are exposed to the direct *risk* of infection at varying ages, chiefly dependent on the above-mentioned factors.

In order to obtain a uniform and comparable material, the beginning of the observation period is calculated from the moment the child is exposed to contagion from the presence of a tuberculous family member. Where, for example, the child has been isolated from the source of infection during the first 2 years of life, the observations period is calculated as beginning from the child's 3rd year.

The same holds for the vaccinated children. Even though the child may be vaccinated immediately after birth and have been isolated during the first 2 years, the observation period as vaccinated is calculated in this case from the beginning of the child's 3rd year; not until this stage is the child exposed to a real risk of infection.

In this manner it is possible to eliminate the significance of isolation to a considerable degree in evaluating the chances of the 2 groups. It is true that the vaccinated children have stayed at the Infant's Home to a greater extent than the con-

trol group; however in the vaccinated group a relatively larger number will be omitted from the Infant's Home material than from the control material, as a large number of those children vaccinated at the Home have not been in contact with infection at all during the period of investigation, and can therefore not be included in the comparison.

When all the children who have not been exposed to actual contact are omitted, the material is considerably reduced. But on the other hand the remaining children form 2 groups which should be comparable in all respects, except that the one group is BCG-vaccinated, and where especially the fact that all the children have really had the possibility of infection is of fundamental significance for the question of BCG-vaccination's effectivity.

From the original material of 293 vaccinated children, there remain in this manner only 181 (68 boys and 113 girls) and of the 400 non-vaccinated control children there remain 394 (190 boys and 204 girls).

For all the children there is information as to sex, date of birth, date of vaccination, age when exposed to tuberculous infection, age when infected and form of the disease. In addition the date and cause of death are known, and in the case of the children lost track of before the end of the observation period ($^{31}/_{12}$ 1941) their age when information stopped.

Of the vaccinated children 48 boys and 34 girls have been under observation both before and after vaccination. As long as they were exposed to tuberculous infection before vaccination they are included in the control group, so that the total number of children under observation in this group is 476 (238 boys and 238 girls).

For both groups the time of possibility of infection through direct contact has been determined in each individual case on the basis of anamnestic information on the child and its milieu, and the age of the child at that time forms the basis of the beginning of the observation period.

For the children who have been exposed to infection during the first year of life, the age at which this occurred has usually been given in months, but for children who first

come in contact with a source of infection after one year of age the time of the beginning of the observation period is given only in whole years.

In regard to infection, a retrospective investigation of this type must necessarily be based on records of others, and it has naturally not been possible to determine the exact time in all of the infected cases. It is often necessary to determine an approximate, not rarely rather long, interval between two examinations. In these cases the determination of the age of infection may be somewhat arbitrary, as this has been evaluated subjectively in consideration of data on the source of infection. For the large majority of the infected however, the infection can be localized to a period between 1 and 3 years, and for practically all who have been infected before the age of 2 years, the time can be determined to within months.

It is much simpler in the cases where the question is to eliminate infection. However in those cases which have not been examined personally, we have often had to accept the report of a negative Pirquet reaction from one or another medical institution (Bureau of Helath, school physician, nurse etc.).

It would have been of interest to investigate the significance of the type of the source of infection in the individual groups, especially the presence of destructive or non-destructive tuberculosis, but with such minute classification of the material the figures would be so small that it would not be possible to draw any conclusions from the results.

For about 30 % of the children in the control group and about 40 % of the vaccinated it was necessary to break off the observation period before 1941 as it was not possible to obtain sufficiently detailed information as to the further fate of the children up to 1941. For these children the observation period is considered concluded corresponding to their age at the last examination. So large a defection from the investigation for the above mentioned reasons is certainly a weakness in the material, as it cannot be excluded that the infection and mortality frequency in these children may later have been so

different from the others that it might have influenced the results. Information on most of these children concludes however with saying that "they are well", but nothing is known as to tuberculin reactions etc. It is therefore safe to assume that there is no considerable morbidity among them.

The table below shows at what age the children have been exposed to tuberculous infection and have come under observation:

Exposed to tuberculous infection at:	Number of cases under observation as:					
	Non vaccinated			BCG-vaccinated		
	Boys	Girls	Total	Boys	Girls	Total
0— 1 years ...	217	216	433	37	22	59
1— 2 » ...	3	2	5	14	10	24
2— 3 » ...	9	5	14	18	12	30
3— 4 » ...	4	4	8	15	9	24
4— 5 » ...	3	4	7	10	6	16
5— 6 » ...	1	2	3	4	2	6
6— 7 » ...	–	2	2	2	2	4
7— 8 » ...	1	2	3	3	1	4
8— 9 » ...	–	1	1	3	–	3
9—10 » ...	–	–	–	2	4	6
10—11 » ...	–	–	–	3	–	3
11—12 » ...	–	–	–	1	–	1
12—13 » ...	–	–	–	–	–	–
13—14 » ...	–	–	–	1	–	1
	238	238	476	113	68	181

Of the non-vaccinated children 427 (213 boys and 214 girls) have been exposed to infection from birth. The BCG treated children were, on the average, somewhat older when they came under observation. 32 % were exposed to infection during the first year of life, 30 % during the ages of 1—3 years, 28 % between 3—7 years and 9 % after 7 years of age.

The following table shows when the children in these groups were vaccinated:

Number vaccinated at n years of age:

Age	Boys	Girls	Total
0— 1 years	56	36	92
1— 2 »	15	8	23
2— 3 »	10	8	18
3— 4 »	5	4	9
4— 5 »	7	5	12
5— 6 »	5	2	7
6— 7 »	2	–	2
7—10 »	8	5	13
10—14 »	5	–	5
	113	68	181

All in all half of the children were vaccinated during the first year of life and 75 % within 3 years of age.

Most of the vaccinated children were exposed to infection the same year that they were vaccinated:

Interval between vaccination and possibility of infection.

	Under 1 year	1—2 years	2—3 years	3 years or more	Total
n children	139	21	17	4	181
%	77	12	9	2	100

It is thus logical to assume, that an eventual vaccination immunity will probably still be present in the majority of the vaccinated at least during the first part of the observation period. The lower infection frequency found in this material in this group of children as compared to the control group must therefore be ascribed to the protective effect of the vaccination.

b. Infected and dead.

211 or 44 % of the non-vaccinated children were infected with tuberculosis during the observation period and 45 or

25 % of the vaccinated. These were distributed as follows according to the type of disease:

Infected children classified according to type of disease.

	Non-vaccinated						BCG-vaccinated					
	Boys		Girls		Total		Boys		Girls		Total	
	n.	dead	n.	dead	n.	dead	n.	dead	n.	dead	n.	dead
1. Tuberculosis occulta	27	–	21	1	48	1	17	–	11	–	28	–
2. Tuberculosis hilii et pulm. primaria	43	[1] 1	72	[3] 5	115	6	6	–	8	–	14	–
3. Erythema nodosum	4	[2] 1	5	–	9	1	2	–	–	–	2	–
4. Keratitis phlyctaenularis	2	–	3	–	5	–	–	–	–	–	–	–
5. Pleuritis tbc.	5	–	4	–	9	–	1	–	–	–	1	–
6. Lymphadenitis colli tbc.	1	–	1	–	2	–	–	–	–	–	–	–
7. Scrofulosis	1	–	1	–	2	–	–	–	–	–	–	–
8. Spina ventosa	–	–	1	–	1	–	–	–	–	–	–	–
9. Scleritis tbc.	–	–	1	–	1	–	–	–	–	–	–	–
10. Tuberculosis ossium	2	–	2	[2] 1	4	1	–	–	–	–	–	–
11. Tuberculosis miliaris	2	2	2	2	4	4	–	–	–	–	–	–
12. Meningitis tuberculosa	3	3	5	5	8	8	–	–	–	–	–	–
13. Tuberculosis pulm. secundar.	1	1	2	2	3	3	–	–	–	–	–	–
Total	91	8	120	16	211	24	26	–	19	–	45	–

[1] Died of tub. pulm.
[2] Died of meningitis tub.
[3] 1 died of tub. mil., 2 of mening. tub. and 2 of non-tub. disease.

In this connection the term "occult tuberculosis" must be discussed.

For the non-vaccinated children the fact is simple, as an

occult tuberculosis means a tuberculous infection which is manifested only by a positive tuberculin reaction,—there are no other clinical or roentgenological indications of tuberculous disease.

For the vaccinated children the term is vague and unprecise. The aim of the BCG-vaccination is to produce a tuberculin allergy without other indications of tuberculous disease, or, in other words, an occult tuberculosis. To determine with certainty when a persisting tuberculin reaction in a vaccinated individual is due to the vaccination, and when it is due to an actual virulent infection is for the present impossible; there are no fully tested methods by which to determine this difference unless when lavage of the stomach shows human tubercle bacillus. It is perhaps logical to take the time element into consideration on this question, since we have seen that a pure vaccination allergy seems to be relatively limited in its duration, while the "true" tuberculin allergy usually persists throughout life. Further some evidence may be found in the intensity of the tuberculin reaction, as vaccination reactions are usually weaker. However in consideration of the large individual variations of the tuberculin reaction in general, it is obvious that a concrete determination cannot be made on this basis in the individual cases.

Relative figures.

	Non-vaccinated			BCG-vaccinated		
	Boys	Girls	Total	Boys	Girls	Total
Occult tuberculosis....	30	18	23	65	58	62
Primary tuberculosis ..	59	70	65	35	42	38
Other forms of tuberculosis	11	12	12	–	–	–
	100	100	100	100	100	100

In 49 of the 181 vaccinated children the tuberculin reaction has become negative during the observation period, and in these cases the possibility of an occult tuberculosis may be excluded. For the remaining 132 children subjective judgment

Infected children classified according to age when infected and type of disease.

Infected at age:	Non-vaccinated				BCG-vaccinated			
	Tub. occult	Primary tub.	Other forms	Total infected	Tub. occult	Primary tub.	Other forms	Total infected
Boys.								
0— 1 years ...	3	15	6	24	–	–	–	–
1— 2 » ...	7	6	–	13	3	2	–	5
2— 3 » ...	5	8	3	16	2	–	–	2
3— 4 » ...	5	9	1	15	2	1	–	3
4— 5 » ...	2	4	–	6	2	–	–	2
5— 6 » ...	–	2	–	2	–	1	–	1
6— 7 » ...	2	3	–	5	2	1	–	3
7— 8 » ...	2	3	–	5	2	1	–	3
8— 9 » ...	1	1	–	2	–	2	–	2
9—10 » ...	–	–	–	–	2	–	–	2
10—11 » ...	–	2	–	2	–	–	–	–
11—12 » ...	–	–	–	–	1	–	–	1
12—13 » ...	–	1	–	1	1	1	–	2
Total	27	54	10	91	17	9	–	26
Girls.								
0— 1 years ...	2	14	7	23	–	1	–	1
1— 2 » ...	5	19	5	29	–	–	–	–
2— 3 » ...	5	15	2	22	–	1	–	1
3— 4 » ...	2	8	–	10	1	1	–	2
4— 5 » ...	2	9	1	12	1	1	–	2
5— 6 » ...	1	5	–	6	2	–	–	2
6— 7 » ...	1	4	–	5	–	2	–	2
7— 8 » ...	1	6	–	7	3	1	–	4
8— 9 » ...	1	2	–	3	3	–	–	3
9—10 » ...	1	1	–	2	–	1	–	1
10—11 » ...	–	1	–	1	–	–	–	–
11—12 » ...	–	–	–	–	1	–	–	1
12—13 » ...	–	–	–	–	–	–	–	–
Total	21	84	15	120	11	8	–	19
Girls + boys	48	138	25	211	28	17	–	45

has been used in the individual cases; this evaluation is based on anamnestic information (the childs general health, eventual periods of fever, the relations to the source of infection, social hygienic conditions etc.) compared with the tuberculin reaction. Where, for example, a strong tuberculin reaction persists for more than 4 years after vaccination, or where a previous "vaccination reaction" shows a markedly stronger reaction in connection with a possibility of infection, for example from a cavernous phthisis, the tuberculin allergy is ascribed to an infection. The same basis of judgment is also used to determine the approximate time of infection.

This subjective evaluation is obviously a weakness in the figures found, but the possibility of an occult tuberculosis for the vaccinated children cannot be excluded by assuming that an existing tuberculin allergy is due exclusively to vaccination.

In the control group occult tuberculosis was demonstrated in 23 % of the infected children, 65 % had a primary tuberculosis in one form or another and 12 % other forms of tuberculous diseases. Primary lung and hilus tuberculosis, erythema nodosum, keratitis phlyctaenularis and pleuritis are all included under primary tuberculosis. Among the vaccinated children the lighter forms of tuberculous infection dominate, and clinical tuberculosis of a more serious nature is not found at all within this group.

It is seen that clinical tuberculosis in both groups is more frequent in girls than in boys.

The following table shows at what age the children were infected. (See table page 39).

In the control group 60 % of the infected acquired the infection before the age of 3 —, 20 % between 3 and 7 and only 11 % between 7 and 13 years of age. Among the vaccinated children however, most of the infections were acquired *after* 3 years of age, namely 38 % from 3—7 years and 42 % from 7—13 years; only 20 % of the infected were under 3 years.

It is true that this difference in age distribution is partly due to the fact that the vaccinated children are older than the non-vaccinated when they are exposed to tuberculous infection, but a longer time elapses from the time of exposure until the time of infection. (Se table page 41).

Infected children classified according to observation year when infected.

Observation year	Non-vaccinated			Vaccinated		
	Boys	Girls	Total	Boys	Girls	Total
1	31	33	64	3	1	4
2	14	35	49	5	3	8
3	17	21	38	6	6	12
4	11	10	21	5	3	8
5	5	8	13	4	2	6
6	–	1	1	3	2	5
7	3	3	6	–	1	1
8	5	5	10	–	–	–
9	3	2	5	–	1	1
10	–	1	1	–	–	–
11	1	1	2	–	–	–
12	–	–	–	–	–	–
13	1	–	1	–	–	–
	91	120	211	26	19	45

Only 9 % of the infected vaccinated children were infected the same year they first came in contact with the source of infection, as against 30 % of the control children who were infected during the observation period. 53 % of the infections

Distribution of deaths among infected children according to cause and age at death.

	0—6 months	6—12 months	1—2 yrs	2—3 yrs	3—4 yrs	6—7 yrs	9—10 yrs	11–12 yrs	Total
Tub. miliaris ..	3	1	1	1	–	–	–	–	6
» meningum	1	4	2	2	1	–	1	–	11
» pulmonum	–	2	1	–	–	–	–	1	4
	4	7	4	3	1	–	1	1	21
Vit. cordis	–	–	–	–	–	1	–	–	1
Pneumococ-sepsis	–	–	–	1	–	–	–	–	1
Appendicit. ac. perforat. c. peritonit. ...	–	–	–	1	–	–	–	–	1
	–	–	–	2	–	1	–	–	3

All unspecific causes of death are verified by post mortem.

among the vaccinated group occur during the 3 first observation years as compared to 72 % in the control group.

In the control group 7 boys and 6 girls died of an unspecific disease without having manifested any signs of tuberculous infection, and 24 children in this group died after they were infected. 21 of these died of tuberculosis. No deaths have occurred among the vaccinated children during the observation period.

c. Infection frequency and mortality.

The figures presented in the preceding section have for the most part only a relative significance, as they are partly dependent on the length of the observation period for each individual. In order to obtain a correct picture of the risk of infection in vaccinated and non-vaccinated children, the number infected in the separate age groups must be compared to the number under exposure to infection in the corresponding age group. By "number under exposure" at a certain age we mean all who are under observation and who have a possibility of being infected at the age in question. The relation between the number of infected and the number under exposure is usually called the infection probability or the infection frequency. Correspondingly: to obtain a correct evaluation of tuberculosis mortality in the material the number of deaths from the disease must be compared to the number of observed individuals who have a chance of dying of tuberculosis during the observation period, — in this case only those who have acquired a tuberculous infection. It is obvious that before this time they cannot die of tuberculosis.

In regard to the calculation of infection frequency and mortality, which are otherwise made in the usual manner, the following should be mentioned:

In the calculation of the infection frequency the children are regarded as having come under observation in the year of age when they came in contact with the source of infection. This age is calculated in months for children under 1 year and after one year as age at last birthday. The latter are calculated as having come under observation in the middle of the year

of age when they were exposed to infection and count for ½ unit in the number under exposure for the year in question.

In calculating the mortality, the observation period is calculated as beginning at the age when the child became infected. This age is calculated as above for children under and over 1 year. A child infected when X years old is assumed to have been infected in the middle of the year of age from X to (X + 1) and is counted as ½ unit in the number under risk of death at the age of X.

In the investigation on the risk of infection each child has been followed from the time it was exposed to infection until the conclusion of the observation period in 1941, or until it became infected or was dropped from the investigation for other reasons before the conclusion of the observation period. In addition to defection due to infection, defection in this material may be due to cessation of sufficient information as to the child or death without tuberculous infection. In the control group there is also defection because of vaccination. The relation to the source of infection (its hospitalization, death etc.) should also be taken into consideration, as the risk of infection is excluded temporarily or permanently by the removal of the source of infection. Sufficiently exact information could not be obtained on this question, and this factor is consequently disregarded

As the observation period in each individual case ends at the latest on the child's birthday in 1941, all the children who are alive and still under observation at the conclusion of the investigation period have been under exposure during the entire year of age which is concluded in 1941. According to the definition of infection frequency given above, also those who are dropped because they become infected are calculated as a whole unit in the number under exposure during the year of age when infection occurred. The same holds true for defection by death in the mortality calculations.

On defection from other causes it has been assumed that those dropped have been under observation during half of the year when dropped, so that they are included as ½ unit in the number under risk at the age in question.

The following table (where boys and girls are included in one group) shows the relation between the infection frequency in BCG-vaccinated children and the non-vaccinated children in the various age groups.

The relation between infection frequency in BCG-vaccinated and non-vaccinated children.

Age in years	Non-vaccinated			B.C.G.-vaccinated			
	No. under exposure	No. infected	Infect. Freq. %	No. under exposure	Observed No. infect.	Calcul. No. infect.	Ratio (5 : 6)
	1	2	3	4	5	6	7
0— 1	376.0	47	12.50	58.0	1	7.2	0.14
1— 2	584.5	80	13.69	134.5	8	18.6	0.43
3— 6	738.5	61	8.26	281.5	17	22.7	0.75
0— 6	1 699,0	188	11.07	474.0	26	48.5	0.54
7—10	334.0	22	6.59	176.0	15	11.2	1.34
11—15	70.0	1	(1.43)	58.0	4	0.7	5.71
7—15	404.0	23	5.69	234.0	19	11.9	1.60
All ages	2 103,0	211	10.03	708.0	45	60.4	0.75

The age groups in this table are the ages which the observed children have passed successively during the period of the investigation.

As the material in this investigation is rather small, it would not be practical to use the directly calculated frequency values as a basis for comparison. Instead the infection frequency has been calculated for boys and girls at the various ages in each group in relation to the average infection frequency of all children of the same age in the control group, which is here used as a common basis for comparison.

By multiplying the calculated number under exposure in the individual age groups with the infection frequency for boys and girls as a whole in the respective age groups in the control material, an expression is obtained of how many children

would have been infected with tuberculosis, if the risk in the group in question had been just as great as in the comparative group. If the actually observed number of infections is divided by the thus calculated number, a ratio is obtained which shows how much lower or higher the infection frequency has been in the group in question than in the comparative group. If, for example the observed number of infected is 4, and the calculated number is 8, this means that the infection frequency of the group in question is only half as high as the average infection frequency in the comparative group.

In the table on p. 44 the number of infected and the number under exposure at the various ages are given for both groups. The infection frequency is calculated for the non-vaccinated children in the various age groups, and with the help of these relative figures the number of infections expected among the BCG-vaccinated children is calculated, if the infection frequency had been the same as in the non-vaccinated children of the same age. It should be pointed out that the latter calculation is made individually for each year of age, and the results summed up to the larger age groups which are presented in the table.

From the directly calculated frequency values, it appears that among the non-vaccinated children the danger of infection is greatest before the age of 3 and sinks rapidly with increasing age. If we calculate the corresponding frequency values for the vaccinated, we find that in this group the absolute infection frequency is greatest after 7 years of age. However the present material is so limited, especially in the higher age groups, that the directly calculated frequency values may to a great extent be influenced by chance factors, so caution is necessary in drawing conclusions on the basis of the absolute figures.

The ratio between the actual number of infected children and the calculated number shows, as mentioned above, the infection risk in the vaccinated group as compared with the control group. Among the vaccinated children who have been exposed to infection during the first year of life, there is 1 child who became infected while the expected figure calculated from the control group is 7. Among the vaccinated children under

observation from the ages of 1—3 years, 8 cases of infection were observed as against 18.6 calculated and in the ages 3—7 years 17 as against 22.7 calculated.

Thus *before* school age the infection risk in the vaccinated children in this material is not more than 54 % of that found for the non-vaccinated children of the same age. This difference between the two groups is so great that it is most probably not due to chance, but must be due to the fact that the BCG-treated children have had greater resistance to tuberculous infection when they are exposed, than the children who have not been vaccinated. Calculation of the mean error of the difference between the observed and the calculated infection frequency for all the vaccinated children under observation between the ages of 0—6 years, shows that the difference between the frequency values is greater than 3 times the mean error.

	0—6 years	7—15 years
Observed infection frequency per 100 exposed vaccinated	5.49	8.12
Calculated infection frequency	10.21	5.09
Difference	4.27	3.03
Mean error of the difference	± 1.29	± 2.09

After the age of 7 the vaccinated children no longer have any advantage over the non-vaccinated when they are exposed to infection. Among the vaccinated in this material who have been under observation after the age of 7 —, 19 cases of tuberculous infection have been observed, and this is higher than the number expected, judging by the control group. However the material in these higher age groups is so small that this may be due to chance. The mean error of the difference between the observed and calculated infection frequency for the ages 7—15 years is, as can be seen, ± 2.09 and the actual difference between the frequency values 3.03, not more than 1.4 times greater.

In judging the infection risk in vaccinated children after

the age of 7, it is important to notice that such a long time has elapsed since most of them were vaccinated, that the protective effect of the vaccine is probably worn off. Of the vaccinated children who have been exposed to infection between the ages of 7 and 13, as many as 40 % were vaccinated before the age of 3 and 68 % before the age of 5 years. On the whole it would have been of interest to determine the relation of infection frequency to the time elapsed since vaccination, in order to elucidate the problem of the duration of an eventual vaccination immunity. But a much more extensive material than the present one is necessary.

In the table below are presented the relative infection frequency values for boys and girls separately, expressed by the relation between the observed and calculated numbers infected:

	Non-vaccinated			BCG-vaccinated		
	Observed no. of cases	Calculated no. of cases	Ratio	Observed no. of cases	Calculated no. of cases	Ratio
Boys	91	108.1	0.84	26	37.7	0.69
Girls	120	102.9	1.17	19	22.7	0.84

Judging from this material it seems that girls are infected more often than boys. This is in agreement with other clinical observations (*Frølich* (1928)). Whether this relation holds in the individual age groups cannot be determined on the basis of this material. If the classes are divided both by sex and age the figures will be too small.

We shall finally present the mortality figures for the infected children. As mentioned above there have been no deaths among the vaccinated children during the observation period. However in the control group 24 of the infected children have died, 21 of these of tuberculous diseases.

The mortality from tuberculosis in this group is as follows:

Tuberculosis mortality among infected non-vaccinated children.

Age	Number under expossure	Number deaths from tuberculosis	Mortality per 100 infected
0—1 years	47.0	11	23.4
1—2 »	148.0	7	4.7
3 years and over	1 133.5	3	1.6
Total	1 328.5	21	1.6

As was to be expected, in this material also the mortality risk for tuberculous infected infants is very high. Almost one fourth of the infected under observation at this age die within the first year of life. In the 2 following years the mortality was much lower, and after 3 years of age quite insignificant.

The deaths which have occurred have had a close connection with the infection, thus 9 died within 3 months after the tuberculous infection was demonstrated, 7 in the course of 4—8 months and only 5 deaths occurred after more than 1 year.

D. Conclusion.

The possibility for tuberculous infection by contagion is much smaller for children vaccinated with BCG than for children who have not been vaccinated. The average infection frequency at the ages 0—6 years is probably only slightly more than half as high for the vaccinated children.

There seems to be a shifting of the time of infection for the vaccinated children, as the infection takes place later in relation to the exposure to infection than in the non-vaccinated children.

The vaccinated children who become infected have a more benign infection than the non-vaccinated.

It seems that girls an more subject to infection than boys, and they develope graver forms of tuberculosis.

In this material none of the vaccinated children have died of tuberculosis, while an average of 1.6 % of the non-vaccinated are dead.

The material is too small to give reliable information as to the duration of the vaccination effect.

About 75 % of the vaccinated children develop a tuberculin allergy, this manifests itself most frequently 40—80 days after vaccination and lasts for about 1 year after the intracutaneous injection of BCG.

PART II.

Some Immune Biological Manifestations in Connection with the BCG-Vaccination.

I. Introductory Remarks.

The significance of the tuberculin allergy for tuberculosis immunity has been the object of much discussion.

From a clinical point of view the solution of the problem meets with great difficulties, chiefly because both properties are found simultaneously, and with our present knowledge it is not possible to isolate them with certainty.

The problem is simpler for laboratory researchers as there is a possibility of separating the qualities and studying them separately in animal experiments. Animal experiments must therefore provide the basis of this interpretation. The clinical impression may then be formed within the limits allowable for drawing analogous conclusions between experimental animals and humans.

It has been demonstrated by *Krause and Willis* (1925) among others that tuberculosis immunity can be acquired. They demonstrated a slower spreading of the tubercle bacilli to the inner organs in re-infected guinea pigs. Since then a large number of experiments have further confirmed this and provided us with a number of details of the immunity mechanism.

An interesting experiment from recent times which also shows that there is an acquired tuberculosis immunity in humans is reported by *Türk* (1942).

2 children (4 and 14 month old idiots) who were BCG vaccinated beforehand (positive tuberculin reaction) were reinfected cutaneously (through a scar) with virulent tubercle bacilli. There was no local reaction and no local swelling of the glands, but in a third non-vaccinated control child a typical primary complex developed with ulceration and local lymphadenitis.

Opinion is divided in two camps on the question of the relation of allergy to immunity.

One group (among others *Krause, Willis, Woodruff, Opie, Zinsser, Ward, Jennings)* interpret the tuberculin allergy to varying degrees as a factor in the increased resistance to infection; they claim that the two properties are completely or partly linked together in their biological effect. The Danes *Jensen, Bindslev* and *Holm* (1935, 1939) agree with them. In inhalation experiments on guinea pigs and subsequent pathological-histological examinations of the lung tissue, they find in the normal animal an extensive, intracellular multiplication of the tubercle bacillus in the pre-allergic phase. When the allergy has developed and an inflammation reaction is released, an inhibition of the growth and spreading of the bacteria is observed. In BCG vaccinated animals which already are allergic when infected, an inflammation reaction occurs around the bacillus, and its growth is inhibited. When the animals were tuberculin desensitized, and the allergy was no longer present, the immunity was also lost as there was uninhibited growth of the bacillus. They conclude that allergy and immunity develope simultaneously and are effective in the same direction by localizing and destroying the bacillus.

Branch and *Enders* (1935) take an intermediate standpoint. They obtained considerable resistance by the injection of killed bacilli, even though the animals in many cases did not become allergic. This shows that allergy is not indispensable for the development of immunity. If comparison is made with other diseases where immunity can be transferred passively (pneumococcous and streptococcous infections), it must be assumed that even though a hypersensitivity developes, this is no proof that there is also an increased resistance.

Calmette first believed that immunity and allergy were intimately related; later he claimed that they were quite independent of each other, and that BCG, even when administered per os, resulted in immunity even when there was no tuberculin allergy. "L'allergie n'est pas une manifestation d'immunité. Elle est exclusivement le signe avertiseur d'une infection bacillaire. L'allergie est un état de l'organism trés different de l'anaphylaxie."

The other group of laboratory researchers who admit that allergy is a factor which accompanies immunity, but who interpret the two phenomena as completely independent of each other, base their views particularly on *Rich's* fundamental experiments. In spirochete experiments he showed that the immunity was transferred passively, but that the hypersensitivity was not transferred (1933), and further immunity could be separated from allergy by desensitization. *Rotschild, Friedenwald* and *Bernstein* (1934) from his laboratory also showed that tuberculous, desensitized animals could be kept desensitized for a long time without loss of immunity when exposed to a virulent infection. A large number of investigators agree in this interpretation and claim that there is no symbiosis between allergy and immunity in tuberculosis,—on the contrary these two conditions are antagonistic, so that an eventual removal of the allergy will lead to an increased immunity. *Birkhaug* also belongs to this group, and has published a number of careful experiments from the BCG laboratory in Bergen in support of his opinion.

In 1933 *Birkhaug* demonstrated a persistent resistance to virulent infection with human bacilli in BCG vaccinated guinea pigs even after a transitory allergy had disappeared. In subsequent years he has made a number of experiments which form the basis of the new conception "*iathergic immunity*". By this *Birkhaug* means the condition of immunity which remains intact after the allergic function has disappeared, either spontaneously or by desensitization with tuberculin. He desensitizes guinea pigs with increasing doses of tuberculin after vaccination with BCG, and by subsequent virulent infection demonstrates that the desensitized, non-allergic animals attain greater immunity than the allergic control animals. The macro- and microscopical changes were also more pronounced in the allergic animals; these show more generalized and more caseo-necrotic tuberculous changes with numerous bacilli, while the virulent infection in the iathergic (non-allergic) animals causes mostly localized, non-caseous tubercles with relatively few bacilli. *Birkhaug* thus claims that the allergic (tissue-destroying, inflammation-stimulating and bacillus-spreading) factor, and the immunity factor (tubercle bacillus-inhibiting and tissue-protec-

tive) are not insolubly connected with each other, although both are developed simultaneously, probably by different antigens in the tubercle bacillus. "We presume that such a strictly immunizing antigen at length will be isolated, inasmuch as we are of the opinion that immunization and desensitization are referable to different antigenic portions contained within the tubercle bacillus." (1939). His experiments thus demonstrate that tuberculin allergy is distinguished biologically from tuberculosis immunity. In a later publication (1941) *Birkhaug* claims to have demonstrated the anaphylactic principle in the BCG tuberculo-protein through animal experiments, also without connection with the immunising effect. *Corper* and *Cohn* (1939) claim a striking quantitative difference between the specific immune and the accompanying allergic or anaphylactic properties in tuberculosis; they claim that these properties must be considered independently in a complete evaluation of human tuberculosis.

We have no concrete experimental results on which to base a *clinical* evaluation of the question of the relation of allergy to immunity. It is to be expected that in the human organism—with its otherwise greater differentiation—these very complicated mechanisms are still further differentiated; everyday life with all the variations of a socalled civilized existence (changes of milieu, variations in exposure, influence of various infectious diseases on the immunity mechanism etc.) must be expected to have some influence, and further it must be remembered that injected infections are man's experimental method of studying immunity and not nature's mechanism. Thus the necessary reservations must be made when experimental results are applied clinically.

However the clinicians are also divided into two camps on this question. A prominent representative of the one group is *Heimbeck* who categorically identifies allergy with immunity (1932). The basis of this is his nurse material from Ullevål Hospital. 4.33 % of the 625 beforehand tuberculin positive became infected after they began working in the tuberculosis wards, while 34.29 % of the tuberculin negative acquired tuberculosis. After BCG-vaccination 2.79 % of those who developed tuberculin allergy after the vaccination became infected,

and 20.57 % of the Pirquet negative. These investigations of *Heimbeck* however have been much discussed, among other reasons because the expression "tuberculous disease" does not seem sufficiently precise *(Birkhaug, Ustvedt, Kayne, Herlitz)*. His results have not been uniformly confirmed by similarly observed material elsewhere (*Mariette*, 1936 among others.)

Aslo *Scheel* (1935), *Kristenson* (1942) and others regard a positive allergy as an expression of immunity, as well as *Flahiff* (1938) who in a favorable observation milieu finds a tuberculosis mortality of 9.9 % for tuberculin negative as compared to 1.9 % for tuberculin positive.

If allergy and immunity were synonymous as *Heimbeck* claims, it would also be expected that there was no immunity when the tuberculin reaction is negative. This is far from the fact. In the first place there most certainly exists a natural immunity of varying degree without a positive tuberculin reaction. This immunity is probably the most important reason why not all who live in a tuberculous milieu do become infected. Moreover cases are known, where the tuberculin allergy disappears in patients who have definitely had tuberculous diseases. *Paretzky* (1936) reports on a material of 80 patients where a previously positive tuberculin allergy disappears and cannot be demonstrated again, even with 10 mg. tuberculin; a number of these patients were constantly exposed to infection. In 2 families he found 3 such cases, and he suggests that this is an expression of hereditary immunity. Some of them showed variation between positive and negative reactions, as did some of the BCG vaccinated in our material. *Koch* (1926) *Anzén* (1939), *Tortone* (1939), *Rosenberg* (1940), *Solem* (1942) et al. have reported similar cases where the tuberculin allergy has disappeared in humans who have previously had manifest tuberculous disease.

In our material we have a case which probably exhibits a clinically iathergic immunity, where a child has been infected and for 8 years on annual control shows negative tuberculin reactions. E. J. no. 387/27, b. $^4/_5$ 27: Source of infection: mother with destructive tuberculosis. The child was placed in the Infant's Home immediately after birth, and remained there until she was 2 years old. During her stay she was BCG vaccinated twice and discharged $^7/_{12}$ 29 with Mant. +. She was then in contact with her mother for a little more than 3 months.

Examination $^{26}/_{6}$ 30 showed a positive Hamburger reaction. In March 1931 she was treated at a hospital for pneumonia of the left lung. She was at the hospital for 12 days, and 2 Pirquet reactions during that time were negative. In Jan. 1932 there was again a weak pos. Hamburger, and roentgenological examination revealed a *small calcification in the right lung.* No particular signs of disease can be found in her history except for the pneumonia in the left lung in 1931.

Subsequently the tuberculin reaction was controlled annually (Pirquet and Mantoux) and was *constantly negative.* Roentgen examination in 1939: Calceous spot in the right lung. New BCG vaccination performed at the Bureau of Public Health, and control examinations since then show constantly positive tuberculin reaction. Latest roentgen examination $^{9}/_{3}$ 42: infraclavicular calcification on the right side.

However it is not certain that the general organ hypersensitivity has disappeared when the skin sensitivity disappears. Cf. the above mentioned experiments of *Freund.* Moreover it has been demonstrated *(Bloch* 1929, *Woringer* 1932 et al.) that in eczema and asthma the skin reacts independently of other tissues.

Wallgren (1933) regards a tuberculin allergy as a criterion of tuberculosis immunity, even though allergy and immunity are not identical concepts. He claims that previously tuberculous children who continue to live in a tuberculous milieu do not become superinfected, — he thus agrees with *Hamburger*'s thesis (1908), that children with a positive tuberculin reaction have a relatively greater resistance to new tuberculous infections. *Wallgren* accepts the consequences of his interpretation by isolating the children after BCG-vaccination until the tuberculin reaction becomes positive. In his latest publication (1942) however, he expresses some change of opinion. He claims here, that a vaccination has taken if a very pronounced local reaction is formed after 6 weeks, even though the tuberculin reaction is negative.

Kjer-Petersen and *Ostenfeld* (1927) have shown that the mortality for infected children who live in an infectious milieu is no higher than for infected children who live in healthy families. *Salomonsen* and *Trætteberg* (1935) have shown that if children with pulmonary tuberculosis survive the first 2 years,—in other words the first clinical manifestations of the disease—the children are to a certain extent safe until the age

of puberty. *Jørgensen and Backer*'s results (1929) point in the same direction.

However a number of other clinical investigations indicate that allergy is not always an expression of increased immunity. From Norway *Frølich*'s investigations (1928) on the prognosis of tuberculosis in children shall be mentioned in particular. Of 2900 7 year old children examined in 1912 he found that 84 % were infected. Re-examination of 1830 of these children 13 years later revealed that 12.2 % had had tuberculous diseases, while 9.3 % of 332 who were Pirquet negativ at the time of the first examination had had clinical tuberculosis. The tuberculin positive children thus show, according to *Frølich*, a certain disadvantage as compared to the negative in a more or less similar milieu. *Lunde* (1933) claims that the allergic individuals develope the most dangerous forms of pulmonary tuberculosis. *Herlitz* (1937) concludes his investigation on the prognosis of occult tuberculosis in children in the same manner as *Frølich*, that tuberculin positive children have a better chance of contracting and dying of manifest tuberculosis than the negative.

In this connection the extensive investigations on South African miners (*Cummins* 1932) should also be mentioned, where the tuberculin positive developed tuberculosis more frequently than the negative. The stronger the tuberculin reaction, the greater was the tendency to tuberculous diseases.

However no uniform clinical agreement between the tuberculin reaction and the degree and intensity of tuberculosis has been demonstrated (*Karen and Danford* 1934, *Lange* 1924) even though some (*Holmes* 1915, *Wingfield* 1934) claim this to be the case. *Frølich* states in 1928: " . . . . und doch bin ich persönlich immer der Auffassung gewesen, dass eine stark positive Lokalreaktion sehr oft der Ausdrück eines aktiven Processes sei."

From America *Stewart* (1933) and *Meyers and Harrington* (1934) claim, on the basis of extensive material (10—20 000 children), the benignity of the primary infection as compared to the destructive, less favorable re-infection in allergic children. The latter authors confirm *Frølich*'s finding: that the tuberculin positive allergic children had 5 times as many tuberculous

diseases as children who, on first examination, revealed a negative tuberculin reaction. *Park* (1933) counters *Stewart* as he finds clinically, that mortality for the positive is about the same as for the negative. He claims that when the tuberculous lesions heal, the chances are no poorer for the positive; the negative on the contrary have the additional risk of a primary infection.

Among the group of clinicians who regard allergy independently of immunity, several have accepted the consequence of their view point and re-introduced tuberculin desensitization in their treatment of tuberculosis,—the Koch tuberculin treatment which awakened such great expectations and caused such bitter disappointment around the turn of the century. *Thompson* (1936) claims recent favorable results with tuberculin desensitization, as do *Bessau and Fernbach* (1932), *Liebermeister* (1937), *Vogt* (1938), *Willis and Jocz* (1939). However tuberculin therapy has not attained any extensive renaissance; for the present reservation should be taken in regard to this two-edged measure in tuberculosis therapy.

In taking a clinical standpoint to the above-mentioned interpretations, it seems logical,—in spite of the many peculiarities which characterize tuberculous infections—to apply our knowledge of bacterial infections in general. We know of a number of infectious diseases where the acquired immunity, wholly or in part, is a fact. This fact holds whether antibodies can be demonstrated or not. In tuberculosis, antibodies can be found in the blood only in the advanced stages of the disease, and even then only to a very limited extent. A humoral immunity mechanism is therefore assumed to be much less significant than the cellular tissue immunity in tuberculosis. Laboratory experiments are enticing because of their exactness, but to reproduce clinically the positive findings which clearly distinguish immunity and allergy in animals has not as yet been possible. Until this has been done, it seems most reasonable to regard a tuberculin allergy as an expression of an undergone infection, which has stimulated the immunisatory functions, whose details are still unknown. Immunity may certainly,

also in humans, be present without tuberculin allergy,—the two concepts are not mutually dependent to such an extent. Whether allergy may exist without immunity,—or whether allergy is a negative immunological factor—we do not know clinically. Our clinical observations indicate that allergic (infected) children in a tuberculous milieu have also acquired an increased resistance to new infections. The investigators of the prognosis of occult tuberculosis who conclude that the positive children have poorer prospects than the negative *(Frølich, Herlitz, Stewart, Myers)* actually compare two non-comparable groups of children. Beforehand the group of negative children must be assumed to be the largest, but of this group only those who *successively* become infected can be compared with those who are already positive,—not the negative group in toto.

An absolutely imperative condition for tuberculous disease is infection; as long as the negative remain uninfected, they have absolutely no chance of becoming ill or dying of tuberculosis. It is not until the negative have been infected that they come on a level with those who have already become positive, and not until then can an eventual comparison of the morbidity and mortality of the respective groups be made. This is particularly emphasized by *Høyer Dahl* (1932), who further points out that social factors and a familial disposition probably influence the positive group disadvantageously, as most of these children are from tuberculous (poorer) homes. *Ustvedt* (1932) finds on re-examination that the previously positive and the previously negative develope clinical tuberculosis with the same frequency, but the morbidity for the newly infected was very much higher than for the previously positive.

The foundation for BCG-vaccination lies in the interpretation that allergy is evidence that immune processes are in activity. The defensive mechanisms of the organism are mobilized by the slight primary infection with the BCG and a relative immunity is assumed to develope subsequently, In a certain number of cases this manifests itself clinically in the form of tuberculin allergy.

In this connection the clinical reports of *Stevenin* and co-workers (1938) shall be mentioned. After 10 years' observa-

tion of perorally BCG-vaccinated children who had been in contact with a tuberculous milieu over a long period they found positive tuberculin reactions in a comparatively *smaller* number of the vaccinated than of the non-vaccinated control material,—a relation which held for all age groups.

II. Personal Investigations.

From the undergone material is seen that only about 75 % of the children were tuberculin positive after the BCG-vaccination. This figure is markedly lower than that of most of the other investigators. We have also demonstrated the better prospects in general for the vaccinated children in infected milieu, — the vaccination has a certain immunizing effect. The question then arises: Is a positive tuberculin reaction after BCG-vaccination a necessary criterion that the vaccination has taken? Are there any clinical signs of immunity without the simultaneous presence or appearance of tuberculin allergy? Are the two concepts allergy and immunity insolubly bound together or are they distinct properties? Statistical investigations of vaccinated children without tuberculin allergy and exposed to tuberculous infection might lead to some results after a long period of observation, but our material in this connection is too limited. However, certain facts in connection with *re*-vaccination indicate a separation of the concepts allergy and immunity.

A. The depth reaction after BCG-vaccination.

1. In non-infected children.

a) Local reaction after injection of live BCG.

The local reaction at the site of inocculation of BCG is well known. The inconsiderable nodule which appears in connection with the intracutaneous injection usually disappears completely after 1—2 days. After some time, most often between 5 and 8 weeks, an infiltration is formed which grows gradually and usually from 2—4 months after the vaccination is about the size of a pea, forms an abscess and often perforates. The cold abscess which is formed developes into a suppurating fistule,

which usually heals with a smooth scar 5—6 months after vaccination. This development varies individually, but abscess formation is seldom seen in children before 2 months after the first vaccination. This appears from the following tables on revaccination. Age and sex do not seem to play any role, but variations in the virulence of the vaccine will probably have some influence. The size of the vaccine dose will probably also have some influence; in 3 of the above-mentioned 4 patients (page 28) where 1 mg. BCG was injected by mistake, there were necrotic reactions after 8, 15, and 56 days.

On revaccination the morphological picture at the site of the vaccination is exactly the same as after vaccination I, but it is striking that the local changes occur much more rapidly.

Of our 293 vaccinated children, 89 were vaccinated 2 or more times. An investigation of these revaccinated children reveals a very regular relationship. This manifests itself in the first place by a *reduction of the incubation period* for the reaction. While after vaccination I the interval between the injection and the time of the appearance of the infiltration at the site of injection is about 5—7—9 weeks, on vaccination II the infiltration developes much earlier. Moreover on revaccination the local reaction is *more intense*, and gives more rapid and frequent development of necrosis. While there is seldom gomme or abscess formation until 2—4 months after vaccination I, necrotic reactions may develope as early as 3—4 weeks after vaccination II.

The reaction time will be still further accelerated on subsequent revaccinations. This manifests itself on the 3rd, 4th and later vaccinations as a reduction of the incubation period down to a few days both for the formation of the infiltration and the development of necrotic reactions. *Brinchmann* pointed this out as early as 1934 in a report on the material of the Infant's Home at that time; he states that after the 3rd and 4th vaccination "as a rule allergy and infiltration (or abscess) occur here practically speaking immediately after the injection." In 1941 *Thorkildsen* reported on 2 ambulantly observed cases where the reaction took place more rapidly after revaccination. There seem to be no earlier reports in the literature on this

regular reduction of the incubation period and an acceleration of the reaction parallel with the number of vaccinations in humans. However *Willis'* animal experiments (1928) with constant re-infection (cutaneous) in guinea pigs with virulent bacilli show the same relationship. This capacity for more rapid reaction on revaccination manifests itself even at intervals of several years between the vaccinations and is seen in both allergic and anergic children; it is practically only those children who did not develope allergy on previous vaccination who have been revaccinated.

The more rapid reaction is also often followed by a more rapid development of the tuberculin allergy, but not always. After revaccination we may often see a positive tuberculin reaction after 1—2 weeks, for example a positive Mantoux reaction as early as 11 days after, a Hamburger after 14 days, a pronounced Pirquet after 18 days etc. In 1928 *Willis* demonstrated a similar reaction in guinea pigs infected with virulent bacilli. On re-infection positive tuberculin reactions were obtained with doses which had previously given negative results.

This characteristic progress of revaccination is presented in Table 1.

In the following tables these abbreviations are used:

Infilt. = infiltration
Necr. = necrotic reaction
Tin. = tuberculin reaction
M = Mantoux O. T.
P = Pirquet
H = Moro-Hamburgers salve test.
f = furuncle
p = pomphus
g = gomme
a = abscess
w = weak

We see here that after vaccination I the infiltration arises after 43—137 days, abscess is formed after 41—154 days, after vaccination II the infiltration after 2—28 days, abscess after 13—36 days, after vaccination III infiltration after 2—3 days, abscess after 3—33 days.

After vaccination I an abscess developes in 9 of 17, after

Table 1. *Depth reactions with live BCG only.*

Child.	Born	Vaccination I					Vaccination II					Vaccination III					Vaccination IV					Vaccination V				
		Date	Dose in mg.	n days after vacc.			Date	Dose in mg.	n days after vacc.			Date	Dose in mg.	n days after vacc.			Date	Dose in mg.	n days after vacc.			Date	Dose in mg.	n days after vacc.		
				Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.
Å 12/26 ♂	19/5 26	17/12 30	0.10	–	–	M ÷	10/10 34	0.10	–	18 a	P ÷ 18															
387/27 ♀	4/5 27	2/10 28	0.05	61	107 g	Mw + 123	19/9 29	0.05	28	–	M ++ 30	17/4 39	0.10	–	11 a	P + 49										
356/28 ♀	23/7 28	8/11 28	0.075 s. c.	61	–	M + 70	18/2 30	0.05 s. c.	13	–	M + 30															
344/28 ♂	26/1 28	4/10 28	0.05	67	77 a	Mw + 107	19/9 29	0.05 s. c.	28	–	Mw + 14															
328/29 ♀	28/4 29	16/11 29	0.05	137	154a	M + 167	28/3 33	0.10	8	30 a	M + 17															
324/29 ♀	11/4 29	16/11 29	0.10	105	152	M ÷	18/2 30	0.05	11	–	Hw + 17	25/9 33	0.05	–	3 a	H + 17	11/3 35	0.10	3	11 a	M + 24					
Å 18/30 ♂	5/7 30	11/1 34	0.10	61	84 a	M + 48	11/3 35	0.10	17	–	M + 24															
Å 15/30 ♂	11/10 30	25/11 31	0.05	92	–	Mw + 61	4/5 32	0.05	21	26 a	H ++ 30	10/9 32	0.05	2	33 a	P + 33	8/5 33	0.05	3	33 a	Pw + 15 P + 20					
Å 27/31 ♂	4/4 31	25/11 31	0.05	57	–	M + 93	4/5 32	0.05	21	30 a	M + 50	8/5 33	0.05	3	15 f	M + 61	11/3 35	0.10	6	12 g	H + 7 months					
Å 70/31 ♀	11/3 31	3/1 34	0.10	–	92 g	M + 69	10/3 35	0.10	3	13 p	M + 24															
Å 209/31 ♀	6/6 31	23/11 31	0.05	61	–	M + 61	4/5 32	0.05	15	21 a	H ++ 14	10/9 32	0.05	2	14 g	H ++ 44										
198/32 ♂	12/8 32	8/5 33	0.04	66	–	÷	25/8 33	0.05	7	–	M + 11 H + 20	10/8 35	0.10	–	–	M ÷	11/11 35	0.10	10	31 g	M + 60	15/10 37	0.10	–	31 a	unknown
Å 29/33 ♂	15/1 33	27/2 33	0.10	–	–	P + 57	26/8 33	0.05	28	–	Hw + 47	10/8 35	0.10	–	12 g	Hw + 19										
Å 30/33 ♂	10/2 33	8/5 33	0.10	43	64 a	M + 51	8/6 34	0.10	9	13 g	Mw + 14															
Å 31/33 ♂	11/11 33	8/6 34	0.10	—	41 f	M + 32	10/8 35	0.10	2	33 f	M + 19															
CV/35 ♂	1/3 35	18/9 37	0.10	72	107	P ÷	1/12 37	0.125	–	36 a	P + 36															
10/39 ♀	24/9 39	27/9 39	0.10	82	–	P ÷ 47	8/3 40	0.10	–	25 a	M ÷															

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vaccination II in 10 of 17, after vaccination III in 6 of 7 and after vaccination IV in 4 of 4.

In case 12/26 the accelerated reaction occurs in spite of an interval between vaccination I and II of $3^{10}/_{12}$ years, for No. 328/29 the interval is $3^{4}/_{12}$ years. For No. 387/27 the accelerated reaction occurs even after an interval of 10 years between vaccination II and III, moreover she becomes Pirquet + although before vaccination III she was Mantoux ÷ and *was nevertheless infected* (roentgenologic calcification, "positive anergie"). In patient 198/32 there was no typical reaction after vaccination III with an interval of about 2 years since vaccination II (poor vaccine?).

In 2 patients (12/26 and 29/33) there was no reaction after vaccination I (the one was tuberculin positive), and yet the accelerated reaction occurred.

As early as 1928 *Wallgren* observed the changes which may occur at the site of injection of vaccination I in connection with a revaccination. It is not rarely seen that there is an *inflammation* of the indolent remains of the first vaccination which may eventually show signs of necrosis. This is also seen in *Table 2*.

These patients also show accelerated revaccination reaction and sometimes more rapid development of tuberculin allergy.

On 8 patients revaccinations were made at very short intervals (7—17 days), experimenti causa. The results are presented in *Table 3*.

Here we see in 3 patients (Å 44/34, Å 39/34, 120/35) a more rapid tuberculin sensitization, and at the same time earlier appearance of infiltrations; in Å 51/35 a necrotic reaction 2 days after vaccination II.

The local reaction after revaccination with BCG exhibits, with its regular occurrence, the same relations as are known on the injection of e. g. non-bacterial albumins and other antigenic substances. On the injection of horse serum the "beschleunigte Reaksjon" is seen *(Pirquet)*, as the incubation period for local or general reaction is reduced parallel with the number of injections. Here also an "Aufflammung" of previous sites of injection is well known. When, for example, egg albumen is injected into the skin of rabbits, the incubation

Table 2. *Reactivation at the site of vacci.*

Child.	Born	Vaccination I				
		Date	Dose in mg.	n days after vacc.		
				Infiltr.	Nekr.	Tin.
XXXIX/26 ♀	21/6 26	20/2 36	0.10	60	cfr. remarks	÷
435/26 ♀	4/5 26	24/1 36	0.10	60	–	÷
10/28 ♂	21/10 28	16/11 29	0.05 s. c.	120 after I 15 after II	140 g after I 50 after II	÷
288/29 ♂	13/4 29	16/11 29	0.05 s. c.	120 after I 24 after II	153 a after I 56 after II	M÷ H÷
324/29 ♀	11/4 29	16/11 29	0.10	105 after I 105 after II	153 a after I 52 after II	÷
198/32 ♂	12/8 32	9/5 33	0.04	66	–	÷
113/35 ♂	4/5 35	10/8 35	0.10 ×2	70	–	÷

nation I on revaccination.

Vaccination II					Remarks
Date	Dose mg.	n days after vacc.			
		Infiltr.	Nekr.	Tin.	
$^{25}/_{5}$ 36	0.10	cfr. remarks		P ÷	Ambulant obs. $^{12}/_{10}$ 36: Activation corresponding to vacc. I. Abscess at 1st but not 2nd site of injection. There are now larger than hazel nut-sized infiltrations at both places with rubor.
$^{30}/_{4}$ 36	0.10	43		?	$^{20}/_{8}$ 36: Pea-sized infiltr., no suppuration. $^{12}/_{9}$: Suppuration corresponding to vacc. I but not to vacc. II.
$^{18}/_{2}$ 30	0.05 s. c.	–	–	M + 30	$^{18}/_{2}$ 30: No infiltr. after I. $^{5}/_{3}$: corresponding to I a linseed-sizeed infiltr., correspond. to II point-sized new infiltr. $^{14}/_{3}$: 2 marked infiltr. $^{9}/_{4}$ incipient abscess formation, bluish-red gomme after I. $^{16}/_{4}$: perforation.
$^{18}/_{2}$ 30	0.05	24	–	P + Hw + 17	$^{18}/_{2}$—$^{9}/_{3}$ 30: No infiltr. $^{14}/_{3}$: 2 palpable infiltr., pea-sized at vacc. I, grain-sized at II, both developed simultaneously. $^{15}/_{4}$: abscess perforated.
$^{18}/_{2}$ 30	0.05	11	–	Hw + 17	$^{18}/_{2}$ 30: No infiltr. $^{1}/_{3}$: 2 infiltr. palpable: I pea-sized, II grain-sized, $^{11}/_{4}$: perforation of abscess after I. $^{5}/_{3}$: infiltr. after I still palbable as pinhead-sized.
$^{25}/_{8}$ 33	0.05	7	–	P+20 M+11	$^{17}/_{8}$ 33: A constant grain-sized infiltr. not perforated. $^{1}/_{9}$: 2 papules. After I renewed inflammation, larger than before and beginning perforation. After II grain-sized papule with bean-sized infiltr. in subcutis.
$^{11}/_{11}$ 35	0.10	17	–	÷	$^{22}/_{11}$ 35: Flat infiltr. like small pea. The 2 others (I) are reinflamed and slightly infiltr. $^{12}/_{12}$: infiltr. after I not palpable.

Table 3. *Revaccination after short interval.*

Child.	Born	Vaccinatio. Date	Dose mg.	n days after vacc. Infiltr.	Nekr.	Tin.	Remarks
256/30 ♀	$^{28}/_{6}$ 30	I. $^{10}/_{9}$ 32	0.05	0			$^{19}/_{10}$ 32: No mark after vacc. I. $^{24}/_{11}$ 33: Ambulant control: 3 infiltr. after vacc., the one on the border of suppuration. H+.
		II. $^{6}/_{11}$ 32	»	24			
		III. $^{25}/_{11}$ 32	»	16			
274/30 ♀	$^{27}/_{9}$ 30	I. $^{28}/_{10}$ 32	0.05	45	64 p	Hw +69	
		II. $^{7}/_{11}$ 32	»	30	0	59	
219/31 ♀	$^{27}/_{1}$ 31	I. $^{11}/_{3}$ 35	0.05	÷	÷		M÷ 8 times, thereafter H+ once (7 months after vacc.). Later M÷ 4 times.
		II. $^{22}/_{3}$ 35	»				
Å-44/34 ♂	$^{11}/_{5}$ 34	I. $^{11}/_{3}$ 35	0.05	14	43 f	M+ 19	$^{25}/_{3}$ 35: Infiltr. after I pinhead-sized, after II bean-sized with marked rubor. $^{23}/_{4}$ 35: I and II equally large, like rice grains and resemble furuncles.
		II. $^{22}/_{3}$ 35	»	2	31 f	M+ 7	
Å-42/34 ♀	$^{29}/_{11}$ 34	I. $^{11}/_{3}$ 35	0.05	44	–	P+ 62	$^{6}/_{8}$ 35: infiltr. disappeared.
		II. $^{21}/_{3}$ 35	»	34	–	P+ 52	
Å-39/34 ♂	$^{10}/_{6}$ 34	I. $^{11}/_{3}$ 35	0.05	45	–	M+ 18	$^{29}/_{3}$ 35: M+++ (inf. and rubor 60 mm.) $^{4}/_{4}$ 35: M+ $^{17}/_{4}$ M? $^{25}/_{4}$ H÷
		II. $^{22}/_{3}$ 35	»	33	–	M+ 6	
Å-51/35 ♀	$^{1}/_{2}$ 35	I. $^{22}/_{3}$ 35	0.05	8			$^{24}/_{4}$ 35: Both infiltr. disappeared.
		II. $^{30}/_{3}$ 35	0.10	2	2 f	÷	
120/35 ♂	$^{14}/_{1}$ 35	I. $^{11}/_{3}$ 35	0.05	42	–	M? 18	A doubtful pos. M. $^{29}/_{3}$ 35, thereafter 4 neg. reactions, then a single weak pos., $^{9}/_{5}$ M÷.
		II. $^{22}/_{3}$ 35	»	31	–	6	

period is shortened and the local reaction intensified parallel to the number of injections. In virus diseases we also meet the same phenomenon in smallpox vaccination: revaccinations give eventually more rapid reactions than primary vaccinations.

This indicates that it is not the live BCG itself which is the cause of this typical revaccination reaction, — the *depth reaction*; it is more reasonable that the phenomenon is dependent on a tuberculoprotein reaction.

For this reason we have made a number of experiments where *killed* BCG are employed in vaccination instead of live. This killed BCG-vaccine was prepared for us by Dr. *Birkhaug* at the BCG-laboratory in Bergen, treated there at 60° for $^1/_2$ hour.[1]

If the same type of reaction occurs when killed BCG are employed, it would be possible to conclude that the phenomenon is due to some substance or other in the tubercle bacillus (protein?) and is not caused by the function of the live bacillus.

b. Clinical experiments with heat-killed BCG.

1. Vaccination I in healthy tuberculin negative children.

14 children from the ages of 2 months to $2^4/_{12}$ years (tuberculin negative) were intracutaneously injected with *killed* BCG in doses varying from 0.00005 mg. to 0.5 mg. As after an ordinary BCG-vaccination a slight infiltration was observed in some 1—2 days after the injection, but a week later only one child (16 months old) had a trace of the vaccination; this was a barely visible infiltration 2×3 mm. In this child (vaccine dose 0.5 mg.) there was a marked inflammation of the infiltration on the 12th day to 10×10 mm., when the site of injection closely resembled a positive Mantoux reaction. After 2 days the reaction began to recede. 21 days after the vaccination this patient had a positive Mantoux, and up to

[1] In the following tables where killed BCG are employed this is marked with a + next to the dose of injected BCG.

Table 4. *Revaccination with*

Child.	Born	Vaccination I.				
		Date	Dose mg.	n days after vacc.		
				Infiltr.	Nekr.	Tin.
114/40 ♀	2/11 40	22/9 41	0.05 +	–	–	M÷
T. S./41 ♀	9/6 41	2/9 41	0.10 +	? 35	–	M÷
K. S./40 ♀	14/2 40	7/5 41	0.50 +	–	–	M÷
K. T./41 ♂	20/3 41	15/8 41	0.10 +	ca. 100 activated at II		M÷
Kj. H./42 ♂	5/8 42	13/8 42	0.10 +	40	–	M÷

that time (discharged) this was a case of a tuberculin allergy which was definitely not caused by infection. On control 3 months later there was a visible scar after the BCG-injection, the tuberculin reaction was still positive (Hamburger), and subsequent control 13 months after the vaccination showed a Mantoux 18×18 while no source of infection could be found in the child's milieu.

In another child (15 months old) vaccinated with 0.05 mg. *killed* BCG, control 9 months later revealed a Mantoux 14×11 after 72 hours. Up to 13 days after the vaccination no local reaction had been observed when she was discharged, while the control examination 9 months later revealed a scar 2×2 mm. No contagious infection could be demonstrated in this case and fluoroscope examination was negative.

Otherwise all of these children had negative tuberculin reactions and no certain local reactions developed later, but it was not possible to control 2 of them.

killed BCG (+) only.

Vaccination II.					Vaccination III.				
Date	Dose mg.	n days after vacc.			Date	Dose mg.	n days after vacc.		
		Infiltr.	Nekr.	Tin.			Infiltr.	Nekr.	Tin.
13/10 41	0.05 +	5	8 p (?)	M÷	5/11 41	0.10 +	7	19 a	M+ 24 H+
3/10 41	0.10 +	15	–	M÷	7/11 41	0.10 +	17	–	M+ 19
10/11 41	0.10 +	9	13 ? p	M÷					
13/10 42	0.05 +	12	49 p 86 g	M+ 88					
16/10 42	0.05 +	5	5 a	M+ 20					

Thus in 2 of 14 children a positive tuberculin allergy was obtained with killed BCG after primary vaccination with 0.5 and 0.05 mg.

2. Revaccination with killed BCG.

Table 4 shows the data on the children revaccinated with killed BCG exclusively.

Of these children, all of whom were tuberculin negative after vaccination I, and where only 2 showed a (somewhat doubtful) local reaction (the other 3 a completely negative local reaction) all 5 developed marked indications of infiltration at the site of injection and 4 of them probably signs of necrosis on revaccination. Moreover in K. T./41 there was an activation of the site of the first vaccination, and he also developed a tuberculin allergy. On vaccination III the time of appearance of the tuberculin allergy is markedly reduced, the reaction time for the appearance of the infiltration is also reduced with a necrotic reaction after 19 days for one of the patients.

Photo 1.

A. B./41 b. $^{21}/_{3}$ 41. Photographed $^{20}/_{10}$ 42 after vaccination VI with 0.10 mg. killed-BCG on $^{10}/_{10}$ 42. Pronounced necrosis after 4 days.

3. Revaccination with live and killed BCG.

Table 5 shows the same results which were demonstrated on revaccination with live bacilli only. Here also it should be remarked that the reactions develope even after several years interval between the vaccinations. (Patient No. 54/37 = $3^{9}/_{12}$ years, No 100/37 = $2^{7}/_{12}$ years, No. 108/37 = $3^{9}/_{12}$ years and No. 109/37 = $1^{8}/_{12}$ years.) After vaccination I we find abscess formation in 4 of 14, after vaccination II in 12 of 14, after vaccination III in 5 of 6 and after vaccination IV in 2 of 2.

The reduced incubation pericd is seen both for the appear-

Table 5. *Vaccination with live and killed (+) BCG.*

Child.	Born	Date	Dose in mg.	Vaccination I			Date	Dose in mg.	Vaccination II			Date	Dose in mg.	Vaccination III		
				n days after vacc.					n days after vacc.					n days after vacc.		
				Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.			Infilt.	Necr.	Tin.
54/37 ♂	22/3 37	15/10 37	0.10	–	105	?	16/7 41	0.05 +	–	26 p 37 a	M + 60					
Å 100/37 ♀	28/7 37	26/8 39	0.10	–	83	M + 21	7/1 42	0.10 +	2	9 a	Mw + as before					
Å 108/37 ♀	3/4 37	15/10 37	0.10	124	–	M ÷	13/7 41	0.005 +	3	24 p	M + 57					
Å 109/37 ♂	16/4 37	5/10 39	0.10	55	–	M + 34	13/7 41	0.005 +	–	24 p	M + 48					
15/39 ♀	24/9 39	28/10 39	0.10	48	–	?	6/3 40	0.10	–	22 a	M + 124	2/5 41	0.5 +	5	17 a	P + 24
Å 109/39 ♀	22/10 39	23/10 39	0.10	30	–	÷	6/3 40	0.10	21	56 a	M + 170	5/5 41	0.5 +	2	14 g	M + 23
Å 117/40 ♂	11/6 40	13/6 40	0.10	–	–	÷	24/9 41	0.05 +	–	21 g	H + 6					
Å 116/40 ♂	5/3 40	15/11 41	0.10	5 s	99 a	M + 67	2/3 42	0.05 +	4	9 a	M+H+ 18					
1a/40 ♀	13/2 40	14/6 40	0.10	35	–	÷	26/8 40	0.10	18	107 g	M? 21 P + 73	12/11 41	0.10 +	5	11 g	M? 8 M + 30
Å 98/40 ♂	29/1 40	6/3 40	0.10	–	90 a	M + 94	26/8 40	0.10	21	21 a	M + 44	12/5 41	0.0005 +	7	7	M + as before
LO/41 ♀	1/10 41	3/10 41	0.10	–	–	÷	12/11 41	0.10 +	56	–	M ÷	20/1 42	0.10 +	7	–	H + 29
AB/41 ♂	21/5 41	26/5 41	0.05	–	–	÷	14/7 41	0.0005 +	–	–	÷	29/9 41	0.05 +	–	5 a	M ? 60
SJ/41 ♂	26/11 41	12/12 41	0.10	47	–	÷	13/3 42	0.05 +	5	9 a	M + 51					
AS/42 ♂	2/2 42	15/4 42	0.10	?	–	÷	6/6 42	0.05 +	3	7 a	M + 7					
AN/42 ♂	12/6 42	13/6 42	0.10	51	–	÷	4/11 42	0.05 +	5	–	÷					
SL/42 ♂	20/8 42	1/9 42	0.10	56	–	H ÷	4/11 42	0.05 +	21	–	÷					
VS/42 ♀	26/9 42	29/9 42	0.10	39	–	÷	13/11 42	0.05 +	3	24 g	÷					
				Vaccination IV					Vaccination V					Vaccination VI		
LO/41		27/3 42	0.05 +	3	7 p	?										
AB/41		7/11 41	0.10 +	–	3 p	÷	7/1 42	0.10 +	15	–	M+ H+ 42	16/10 42	0.10 +	3 Photo no. 1	3 a	M + 28

Revaccination with minimum quantities of killed BCG (+).

				Vaccination I			Vaccination II									
OS/41 ♂	22/1 41	5/11 41	0.10	–	63 a	M+H+ 65	18/6 42	0.00005 +	14	39 g ? 52 a	H + 33					
KS/41 ♂	21/4 40	11/6 41	0.10	42	61 g	M + 42	18/6 42	0.00005 +	18	–	+ as before					
PN/42 ♂	6/2 42	15/4 42	0.10	–	42 g	M + 51	18/6 42	0.00005 +	12	39 a [1]	+ as before					

[1] Former BCG remains reinflamed 15×15 mm. with necrosis 3×5 mm. 13/6 this site was crusty.

Table 6. *Peroral vaccination with parenteral revaccination.*

Child.	Born	Vaccination I		Vaccinacination II (and III)				
		Date	Tin.	Date	Dose mg.	n days after vacc.		
						Infiltr.	Necr.	Tin.
462/26 ♀	13/12 26	22/6—28/4 27	÷	19/9 29	0.05 s. c.	–	–	÷
455/26 ♂	28/5 26	15/6—23/6 27	After 2 months sporadicallypos.	15/11 37	0.125	32	–	÷
467/26 ♂	7/9 26	22/6—28/4 27	M+ twice, otherwise neg.	5/12 35	0.10	46	46 a	P+ 46
468/26 ♀	13/12 26	11/6—30/6 27	M+ once, otherwise neg.	18/9 29	0.05 s. c.	–	–	÷
Å 25/31 ♀	29/6 31	1/3 34	÷	10/6—14/6 35	peroral	–	–	÷
—»—	–	–	–	9/6 34	0.10	40	102 a	÷

ance of infiltration and for the formation of abscesses, and in 1 case there was a positive Hamburger after 6 days.

It should also be noticed that depth reactions occur with *killed* BCG in very small doses (patient 98/40 where there was a reaction after 0.0005 mg.). The 3 children where 0.00005 mg. doses were employed show that even minimum doses give the same reaction picture. (These very dilute BCG-solutions were also prepared by *Birkhaug.)* All of these showed a characteristic reaction, in P. N./42 there was also a focal reaction.

These characteristic reactions after revaccination, *the depth reactions*, are found in 41 of the 89 revaccinated children in the BCG-material. In 19 there was a doubtful depth reaction, due to some extent to insufficient observation. 9 of the revaccinated have been partly vaccinated perorally, and it is probable that the absence of depth

reactions in these is an expression of the ineffectivity of the peroral vaccine, as no sensitization had taken place (see Table 6).

In 20 more of the 89 the depth reaction is negative. If we analyse these vaccinations we find that one and the same vaccine ("Norwegian 0.02") has been used for the first or subsequent vaccinations no less than 9 times (3 times with positive Pirquet, 6 times negative). In 4 cases one and the same Swedish vaccine (Gothenburg 22) was used, and in 2 cases vaccine "No. 27". It is logical to assume that poor vaccines are to some extent responsible for this absence of the reactions, since so many children vaccinated with the same vaccine do not exhibit the otherwise usual depth reaction on revaccination.

The supplementary experiments with killed BCG were made on children now at the Infant's Home (mostly between the ages 0—1 years) and not included in the above described material of vaccinated children.

2. *BCG-injection in infected children.*

a. Live BCG.

2 tuberculosis infected patients about 1 year old were injected intracutaneously with 0.10 live BCG. In one a furuncle developed after 2 days which healed rapidly and was barely palpable after 8 days. In the other, who had marked gommes scrophuleux on the neck with some perforations, a peasized abscess with an almost fig-sized infiltrationd eveloped after 1 week. (Progress parallel with *Heimbeck*'s experiment in 1927). At the same time there was a marked impression of a *focal reaction* in the very pronounced gland swelling, which developed in the course of 1—2 weeks and later receded. 4 weeks after the vaccination the abscess was healed and the infiltration after the BCG-injection had disappeared.

None of the patients exhibited any general reaction to the vaccination: temperature curve unchanged, sedimentation rate (Landau) constantly high both before and after.

In the scrophulous patient there was a marked impression 4 weeks after the vaccination that the glands were reduced in size, and the subsequent improvement in general condition was surprisingly rapid.

Table 7. *BCG-vaccination in infected children.*

Child.	Born	Vaccination		Reaction after 1 week	Diagnosis
		Date	Dose in mg.		
B. S. ♀	$^{11}/_{3}$ 40	$^{28}/_{3}$ 41	0,10	Healing furuncle	Infiltr. pulm. bilat.
A. J. ♀	$^{18}/_{1}$ 40	$^{17}/_{1}$ 41	0,10	Pea-sized abscess	Scrofulosis.
T. E. ♀	$^{7}/_{7}$ 39	$^{2}/_{5}$ 41	0,5 +	15×25 mm. pustule.	Infiltr. pulm.
T. K. ♀	$^{7}/_{11}$ 41	$^{26}/_{3}$ 42	0,05 +	15×10 mm. abscess	Tub. miliaris
S. J. ♂	$^{16}/_{3}$ 41	$^{30}/_{3}$ 42	0,05 + 0,0005+ 0,00005+	15×10 mm. 15×10 mm. 8×6 mm.	Tub. miliaris.
E. O. ♂	$^{7}/_{11}$ 38	$^{19}/_{5}$ 41	0,00005 +	3×3 mm.	Infiltr. pulm.

b. Heat-killed BCG.

In the 4 other infected patients (ages $^{5}/_{12}$ and 2 years), varying doses of *killed* BCG were injected intracutaneously.

The results of BCG-injection on the infected children are presented in Table 7.

For the infected vaccinated for the first time the conditions are the same as for revaccinated BCG-children, but the reactions are stronger. After 1 week strong reactions develope, usually necrotic. In the course of 6 weeks all of the reactions became necrotic except the one where 0.00005 mg. was used. In pus from 2 of the abscesses (from patients with miliary tuberculosis), tubercle bacilli were found, but cultivation on Løwenstein medium gave no growth and inocculation into guinea pigs was negative.

Photo 2.

M. K.'s son, b. $^{12}/_{4}$ 43 (Pat. II, Table 8): BCG vaccinated $^{13}/_{4}$ 43, photo taken $^{23}/_{4}$ 43 shows necrotic reaction 10 days after vaccination. Mother BCG vaccinated $^{6}/_{3}$ 43 (0.05 mg. BCG i.c.).

Nor was there any sign of general reaction in these children in connection with the BCG-vaccination.

Thus the infected children show the same accelerated reaction regardless of whether live or killed BCG are employed.

3. Transplacental transmission of the depth reaction's mechanism?

On the assumption that this depth reaction is caused by the tuberculo-protein in BCG, it is to be expected that the basis of the mechanism—eventual antibodies—might be transmitted passively via the placenta.

This should be clinically demonstrable by BCG-vaccination of tuberculin negative mothers during the last part of pregnancy. If the newborn child shows an accelerated local reaction on its first BCG-vaccination, this might be proof of the transplacental transmission of the mechanism of the depth reaction.

Table 8. *Control children vaccinated when newborn.*

Child.	Born	Tuber-culosis in family	BCG.vaccinatio				Remarks
			Date	Dose mg.	n days after vacc.		
					Infiltr.	Necr.	
S. M. ♀	$^{23}/_{10}$ 39	mother	$^{25}/_{10}$ 39	0.10	32	–	$^{17}/_{11}$ 39 no mark. $^{29}/_{11}$ grain-sized infilt. $^{15}/_{12}$ as before. $^{16}/_{1}$ 40 unchanzed. M ÷. Revacc. $^{29}/_{3}$ 40.
L. O. ♀	$^{1}/_{10}$ 41	?	$^{4}/_{10}$ 41	0.10	–	–	Up to $^{11}/_{11}$ no mark after BCG. H÷ $^{29}/_{10}$ M÷ $^{26}/_{10}$. Revacc. $^{11}/_{11}$ 41.
A. B. ♂	$^{21}/_{5}$ 41	mother	$^{28}/_{5}$ 41	0.10	–	–	$^{1}/_{6}$, $^{23}/_{6}$, $^{24}/_{7}$ no local reac. M÷. Revacc. $^{14}/_{7}$ 41.
A. N. ♂	$^{12}/_{8}$ 42	father	$^{15}/_{8}$ 42	0.10	51	–	$^{5}/_{8}$ grain-sized infiltr. after vacc. $^{1}/_{11}$. No mark. H÷ $^{6}/_{7}$, M 8×8 $^{22}/_{7}$.
S. L. ♂	$^{29}/_{8}$ 42	?	$^{1}/_{9}$ 42	0.10	25	–	$^{26}/_{9}$ barely visible mark after vacc. $^{19}/_{9}$ M÷. Revacc. $^{4}/_{11}$.
V. S. ♀	$^{26}/_{9}$ 42	mother	$^{29}/_{9}$ 42	0.05	39	–	$^{20}/_{10}$ no infiltr. $^{7}/_{11}$ pinhead-sized infiltr. M÷ $^{3}/_{11}$. Re-vacc. $^{13}/_{11}$.

With this aim in view 6 mothers were vaccinated 2—8 weeks before partus. In addition 1 newborn child was vaccinated, whose mother was vaccinated in 1938: this mother was Mantoux + on examination without ever having had any signs of tuberculous disease. However in all probability her positive tuberculin reaction was due to an infection allergy. She had been a nurse for some years after her BCG-vaccination.

The result of this investigation is presented in Table 9.

The tuberculin examinations of these children have been made both with 1 mg. Old-tuberculin and with $^{1}/_{500}$ mg. purified

BCG-tuberculin; in addition the so-called "BCG-plaster" has been applied on the sternum. This is "Astra's" control plaster for percutaneous tuberculin tests, where a few drops of killed BCG-culture (100 mg. per cc.) are rubbed into the plaster. (Cf. below under percutaneous tests, page 81.)

The infiltrations in these children appear much earlier

Table 9. *Vaccination of newborn whose mothers*

No.	Mother				Partus	
	Age	BCG		Tin+ 1943	Date 1943	Tin÷ BCG-plaster÷
		Date 1943	Dose mg.			
I.	$^{24}/_{1}$ 16	$^{22}/_{1}$	0.05	$^{3}/_{3}$	$^{27}/_{2}$ ♀	$^{3}/_{3}$
II.	$^{9}/_{7}$ 22	$^{6}/_{2}$	0.05	$^{16}/_{4}$	$^{15}/_{4}$ ♂	$^{16}/_{4}$
III.	$^{26}/_{3}$ 22	$^{27}/_{4}$	0.10	$^{26}/_{5}$	$^{24}/_{5}$ ♂	$^{26}/_{5}$
IV.	$^{17}/_{5}$ 19	$^{28}/_{4}$	0.10	$^{11}/_{6}$	$^{6}/_{7}$ ♂	
V.	$^{23}/_{5}$ 25	$^{15}/_{5}$	0.10	$^{21}/_{6}$	$^{29}/_{5}$ ♀	$^{21}/_{6}$
VI.	$^{8}/_{10}$ 25	$^{29}/_{5}$	0.10	$^{14}/_{7}$	$^{9}/_{7}$ ♂	$^{14}/_{7}$
VII.	$^{16}/_{3}$ 16	1938	?	$^{15}/_{5}$	$^{23}/_{7}$ ♂	

*) Information on vaccination result based on observations by out-of-

than after primary vaccination in other newborn children, and similarly necrotic reactions develope earlier. The lack of necrotic indications in children Nos. 1 and 3 is probably due to intercurrent illness and debility, which must be assumed to influence the rate of reaction. In No. 5 necrosis has not been demonstrated with certainty but the infiltration appeared as early

were vaccinated during pregnancy.

Child.				Remarks
BCG		n days after vacc.		
Date 1943	Dose mg.	Infilt.	Necr.	
$^{6}/_{3}$	0.10	11	–	*) $^{17}/_{3}$ and $^{24}/_{3}$. Shot-sized infiltr. Mors pneumoni $^{4}/_{4}$.
$^{18}/_{4}$	0.10	9	9 a	$^{7}/_{5}$: perforated, crusty. Photo No. 2, $^{23}/_{4}$.
$^{27}/_{5}$	0.10	7	–	Sepsis neonat. $^{3}/_{6}$ and $^{14}/_{6}$ still marked infiltr. $^{15}/_{7}$ barely visible mark, no perforation.
$^{2}/_{6}$	0.10	7	–	*) $^{9}/_{6}$ small but definite infiltr. $^{16}/_{6}$ grain-sized. $^{26}/_{6}$ as before with reddish-blue discoloration. No perforation.
$^{21}/_{6}$	0.025	7	7 p?	$^{28}/_{6}$ infiltr. 3×4 mm. shiny. $^{14}/_{7}$ insignificant infiltr. like a smal pigment spot. No perforation.
$^{15}/_{7}$	0.10	5	–	*) $^{20}/_{7}$ grain-sized infiltr. 2×3 mm. $^{26}/_{7}$ red-brown spot 2×2 mm. $^{2}/_{8}$ as before. $^{23}/_{9}$ unchanged.
$^{26}/_{7}$	0.10	50	–	$^{3}/_{8}$, $^{11}/_{8}$, $^{18}/_{8}$, $^{25}/_{8}$: no infiltr. $^{15}/_{9}$ slight superficial infiltr. 2×3 mm. with brownish color.

town physicians.

as 7 days after the vaccination in spite of the fact that only 0.025 mg. BCG was employed.

Patient No. 7 shows no accelerated reaction, probably because his mother was vaccinated so long before as 1938. He shows the usual reaction after primary BCG-vaccination in newborn, which also appears from the control children in Table 9.

For the sake of completeness experiments should also have been carried out with *killed* BCG in both mothers and children. However the difficulty in obtaining sufficient suitable experimental objects prevented this. As is reasonable, all experimentation during the last months of pregnancy is met with considerable scepticism especially when injections are involved.

Beside the inconstant and—compared with the tuberculin reaction after virulent infection—generally weaker tuberculin reaction after BCG-vaccination another skin reaction also appears, — a regularly characterized depth reaction.

This depth reaction shows the same peculiarities as ordinary bacterial allergy. It may be assumed that it is due to the introduction of tuberculo-protein in the organism. In this connection it would have been logical to experiment with pure BCG-tuberculo-protein but this was impossible to obtain under the present circumstances.

It is logical to regard this protein reaction as *Koch*'s phenomenon, which might be interpreted as an expression that the tissue of the organism has developed a relative immunity to the tubercle bacillus. But the fact that the infiltrations continue to develope without being completely suppressed after a short time with rapid resorbtion does not agree fully with *Koch*'s original description: "Wenn ein bereits tuberkulös erkranktes Meerschweinchen injisiert wird, verklebt die kleine Impfwunde auch anfangs, aber es bildet sich kein Knötchen, sondern schon am nächsten oder zweiten Tage tritt eine eigentümliche Veränderung an der Impfstelle ein. Dieselbe wird hart und nimmt eine dunklere Färbung an, und

zwar beschränkt sich dies nicht allein an die Impfstelle selbst, sondern breitet sich auf die Umgebung bis zu einen Durchmesser von 0.5 bis 1 cm. aus. An den nächsten Tagen stellt sich dann immer deutlich heraus, dass die so veränderte Haut nekrotisch ist, sie wird schliesslich abgestossen, und es bleibt dann eine flache Ulceration zurück, welche gewöhnlich schnell und dauernd heilt, ohne dass die benachbarten Lymfdrüsen infiziert werden."

The comparatively protracted course of the reaction, at least after the first revaccination, does not agree completely with the description of Koch's phenomenon, and moreover the general symptoms are lacking.

As mentioned in the introductory remarks, the dissociation of the tubercle bacillus into various fractions with differing specific properties has been demonstrated by several laboratory investigators. Judging from the findings in animal experiments we might interpret these clinically demonstrated and fully described reactions—the tuberculin reaction and the depth reaction—as caused by different specific antigens in the tubercle bacillus. The reactions differ in their expression and may occur simultaneously or independently of each other. The tuberculin reaction is the prototype of an allergic reaction, while the depth reaction also exhibits other characteristics; similar to reactions after the injection of non-bacterial protein, it exhibits a reduction of the incubation period and an intensification of the local process on reinjections, an "Aufflammung" of previous sites of injection, and its mechanism can be transmitted transplacentally. In its nature the depth reaction is probably also an allergic reaction, since it does not occur momentarily like an anaphylactic reaction, — nor does it recede as rapidly as an urtica blister; its course is much more protracted, and the skin reaction developes into necrosis. But its mechanism can be transmitted transplacentally and is thus distinguished particularly from the typical allergic tuberculin reaction. On the basis of this transmission—a passive sensitization—one might assume that the reaction is caused by demonstrable antibodies, and this is, according to *Wells*, a criterion of an anaphylactic reaction. Insofar as this goes, it is possible to say that this reaction type

is *anaphylactic-like*, even though the reaction has not otherwise the acute and intense characteristics of the anaphylactic reaction. In this connection the fact must be taken into consideration, that the manifestations of hypersensitivity have individual peculiarities in different species of animals, and that some animals are more readily sensitized than others; identically reacting substances which presumedly have the same reaction mechanism, can manifest themselves differently in rabbits and guinea pigs for example. This is ascribed to variations in the capacity to form antibodies and to variations in the relative quantity of antibodies in the tissue fluids and cells. In humans there is a relatively slight tendency to acute, general, anaphylactic shock, while the tendency to a localization of the manifestations in the individual tissues is more pronounced. Many of the problems which form the basis of the clinical manifestations of human hypersensitivity can therefore probably only be solved by investigations on humans,—animal experiments are insufficient.

The depth reaction which partly acts independant of the tuberculin reaction might indicate there is an immunity to tuberculosis even though there is no demonstrable tuberculin allergy.

On the basis of the present findings we believe that a positive tuberculin reaction is not necessary in order that a BCG-vaccination be considered effective. A positive depth reaction is probably a better criterion.

Summary.

After revaccination, reactions occur at the site of injection which are morphologically similar to reactions after primary vaccination, but they regularly appear with reduced incubation period and more rapidly developing necrotic reactions parallel to the number of the vaccinations. The phenomenon persists even when the interval between the vaccinations is of several years. Further revaccination often leads to focal reaction—reactivation—at the site of the first vaccination, and the tuberculin allergy may develope much more rapidly than otherwise, 6—18 days after revaccination.

It is probable that this reaction type — *the depth reaction*—is determined by the tuberculo-protein in the BCG. It is found that exactly the same reaction type occurs when *killed* BCG are employed, either alone or alternating with live bacilli. In 2 cases tuberculin allergy was obtained after primary vaccination with killed bacilli.

In *infected* individuals the accelerated reaction occurs on primary injection of BCG, both with live and killed vaccine.

The mechanism of the depth reaction can be transmitted via the placenta.

B. Cutaneous Tests.

a) BCG-tuberculin.

It would seem logical to expect a more specific tuberculin reaction on the vaccinated children when BCG-tuberculin is used. The Veterinary Institute prepared a BCG-tuberculin for us in the summer of 1942 and it was prepared in the same manner as ordinary Old-tuberculin, with the BCG as a starting point.

On 4 vaccinated children aged 7 months, 7 months, 10 months and $2^{5}/_{12}$ years, scratch reactions after Pirquet were made ($^{5}/_{9}$ 42) with Old-tuberculin and with BCG-tuberculin with the following results:

	Child	I	II	III	IV
2 days	BCG	0.0	0.0	1.1	1.0
	OT	3.3	2.2	3.3	0.0
3 days	BCG	0.0	0.0	0.0	0.0
	OT	3.3	0.0	2.2	0.0
4 days	BCG	0.0		0.0	
	OT	3.3		2.2	

The figures represent rubor and infiltration in mm.

In addition intracutaneous reactions were carried out on one child (10 months old) on $^{19}/_{9}$ 42 with 1 mg. Old-tuberculin and 1 mg. BCG-tuberculin:

	OT	BCG
2 days	12×15 mm.	12×15 mm.
3 days	15×18 mm.	12×15 mm.
4 days	10×10 mm.	5× 5 mm.

In 2 other vaccinated children (2 and 4 months old) on $^{3}/_{10}$ 42, 1 mg. BCG-tuberculin was applied intracutaneously; after 2 days these reactions measured 8×8 mm. and 10×10 mm. respectively, the latter pale without rubor. On the 3rd day the reaction was completely negative in both. However previously after reactions with 1 mg. Old-tuberculin ($^{23}/_{9}$ and $^{23}/_{9}$) and after BCG-tuberculin ($^{23}/_{10}$ and $^{11}/_{11}$) these children also gave negative reactions.

This does not seem to indicate any specificity for the BCG-tuberculin. However *A. Lind* in December 1942 gives a preliminary report on a number of interesting experiments with *purified BCG-tuberculin* prepared at the State Serum Institute at Copenhagen. According to him the BCG-tuberculin proves to be 4 times weaker than the purified human tuberculin through human standardization. Nevertheless *Lind* claims much more extensive and sharply limited reactions than with purified human tuberculin in BCG-vaccinated individuals. Some of the vaccinated were *negative* with human tuberculin, but gave a marked reaction (12×15 mm.) with the same or a smaller quantity of purified BCG-tuberculin. He concludes that a BCG-vaccinated individual has not necessarily lost all allergy, even if he no longer reacts to ordinary tuberculin. *Lind* thus assumes a specific effect of BCG-tuberculin as compared with Old-tuberculin in vaccinated individuals.

Our investigations in this connection are so few in number that they may not justify the exclusion of such a specificity, but with the tuberculin we had at our disposition the results were uniformly negative. We have since made comparative experiments with purified BCG-tuberculin obtained through the kindness of *Lind*, with the following results:

10 children from $^{1}/_{2}$—$2^{1}/_{2}$ years. 1 mg. OT in 0.10 cc. saline intracutaneously on rt. overarm and $^{1}/_{500}$ mg. purified

BCG-tuberculin in 0.10 cc. saline on left overarm. Rubor and infiltration recorded in mm.

Child	I	II	III	IV	V	VI	VII	VIII	IX	X
BCG	10.10	14.10	10.10	12.10	10.12	14.8	7.8	8.8	14.16	15.15
OT	12.10	10.10	12.10	8.10	5.4	10.12	10.10	8.8	12.10	12.14
2 days										
BCG					8.6	8.6	5.5	5.6	10.8	10.8
OT					2.3	10.8	6.6	7.5	10.8	10.10
3 days										
BCG	10.10	10.12	10.10	÷	8.5	8.6	4.4	5.4	10.10	12.10
OT	10.10	8.8	10.10	8.8	÷	10.8	6.6	6.6	10.8	15.12
4 days										

After 2 days the BCG-tuberculin gives a stronger reaction in 6, in 3 the OT is stronger. After 3 days the BCG is stronger in 1, OT in 3. After 4 days BCG is stronger in 3, OT in 5. Otherwise the reactions are identical. No pronounced difference can be demonstrated. However child V is remarkable (Table 5, pat. A. B./41). He was vaccinated 6 times without showing any tuberculin allergy; here the BCG-tuberculin gives a much stronger reaction than OT.

Examination was made every day for *focal reaction* in the BCG-scar but this was never observed, not even in child V where the BCG-tuberculin was injected between the scars of the 6 previous vaccinations.

b) Percutaneous Tests with Killed BCG.

As shown in the foregoing the tuberculo-protein specific BCG-reaction—the depth reaction—appears even with minimum quantities of antigen (0.00005 mg.). This reaction form is perhaps more frequent than the tuberculin allergy.

As no pronounced specificity for BCG-tuberculin could be demonstrated in the vaccinated children, this led to the trial of killed BCG in the skin tests. The difference between BCG-tuberculin and killed BCG is not great, as killed BCG also form the basis of BCG-tuberculin. However in the latter

case, in addition to being heat killed, the bacilli are also chemically (perhaps also physically?) influenced by the glycerine and peptone which are added.

Preliminary experiments were made to compare Old-tuberculin and emulsions of killed BCG in various concentrations with *skin scratches* after Pirquet. In both 4 patients with active tuberculosis and 3 children who were BCG-vaccinated, the reactions were decidedly stronger for OT. In 2 adults with latent infections (tuberculin positive without disease) however, the skin reaction with BCG appeared to be stronger than with OT as it was of longer duration and became reinflamed after 1 week. In these 2 the scratches with tuberculin and BCG were covered with plaster for 24 hours, while in the 4 above mentioned, ordinary air drying for 10 minutes was employed.

3 vaccinated and as control 1 infected child[1] were then tested *without* any scratch (on ether-washed skin on the sternum) with 1 drop of Old-tuberculin and 1 drop of killed BCG-emulsion in concentration 10 mg. per cc. The drops were covered with ordinary plaster (leucoplast), which was removed after 3 days.

In 2 of the vaccinated there was a skin reaction both under the BCG-plaster and under the tuberculin plaster, and these reactions were about equally strong on the 4th and 5th day. In the 3rd the BCG was negative after 5 days, the tuberculin plaster showed a positive reaction. The infected patient had a strong reaction to tuberculin, the BCG-plaster was torn off.

The experiment was repeated with 2 vaccinated, 2 infected and 1 unvaccinated healthy control child. This time we used the *control plaster* in the Swedish factory for pharmaceutical preparations "Astra"'s tuberculin plaster, by rubbing the killed BCG (10 mg./cc.) into the plaster mass with a glass rod,—about 2—3 drops to each plaster which is slightly under 1 cm.^{2}. As tuberculin test "Astra's" tuberculin plaster was used which is said to contain 1 drop of tuberculin (OT). All the plasters were removed after 2 days. 4 and 5 days after the tests were

[1] In this and all subsequent experiments children aged 6 months to 4 years are used.

made the result again showed about equally strong positive reactions for tuberculin and BCG in the vaccinated children; the infected showed a markedly stronger reaction for OT. In the control there were no reactions to either.

These preliminary experiments indicated that there is a difference between the percutaneous reaction after OT and killed BCG in vaccinated and infected.

For this reason we made experiments on a larger scale, but found it practical to use higher concentrations of BCG (100 mg. per cc.) than previously. When rubbing in the emulsion by hand (Astra's control plasters are used here) we had the impression, that the BCG was difficult to mix with the plaster mass. Otherwise the technique is the same as in the preliminary experiment above with Astra tuberculin plaster which was removed after 2 days.

Table 10 shows the same results as those indicated by the preliminary experiment: in the infected children the plaster with tuberculin generally shows a much stronger reaction than the BCG-plaster, while in the vaccinated children the reactions are equally strong or the BCG-reaction is more pronounced.

In 3 vaccinated children (Nos. 11, 16 and 19) this was however not the case, as the OT reaction was stronger than the BCG. A careful review of their histories revealed remarkable facts.

Patient No. 11. Girl, b. $^{31}/_{1}$ 38. Stayed at the Infant's Home $^{27}/_{3}$ 38 to $^{5}/_{10}$ 42. Mother had destructive tuberculosis and paternal grandmother also was infected. The child had whooping cough on admission but otherwise seemed in good health. Mantoux neg. $^{30}/_{5}$, $^{3}/_{6}$, and $^{21}/_{6}$ 38. Roentgen examination $^{3}/_{6}$ 38 showed a doubtful hilus congestion on the rt. side. This was however not interpreted as specific, partly because the tuberculin reactions were negative, partly because her whooping cough could explain an unspecific infiltration in the hilus. The possibility of a whooping cough anergy was not sufficiently considered. She continued to thrive with rapid recovery from whooping cough, and $^{25}/_{11}$ 38 she was BCG-vaccinated. No tuberculin tests were made between $^{21}/_{6}$ and the vaccination $^{25}/_{11}$ 38. On $^{10}/_{2}$ 39, about 3½ months after the vaccination, the tuberculin reaction was positive, and since then all her tuberculin tests have constantly been positive during her entire stay at the Home ($3^{7}/_{12}$ years). There is a possibility that she had an infection allergy, as the last neg. tuberculin tests before vaccination may be explained either by her whooping cough, or they may have

Table 10. *Patch tests with killed BCG (100 mg. pr. cc.) and Old-tuberculin.*

Child.	Days after patch test was made	Vaccinated		Infected		
		Tin.	BCG	Tin.	BCG	
1 ♂	3	+	+			
	5	+	+			
2 ♀	3	+	+			
	5	+	++			30/9 42.
3 ÷ ♂	3	+	+			
	5	÷	÷			
4 ♀	3			+++	+	
	5			+++	+	
5 ♀	3	+	+			
	4	++	+			
6 ♀	3	+ (?)	+ (?)			
	4	+	+			
7 ♀	3	+ (?)	+ (?)			
	4	+	+			29/8 42.
8 ♀	3	+	++			
	4	+	++			Photo No. 7.
9 ♂	3	++	++			
	4	++	++			
10 ♀	3			+++	+	
	4			+++	+	
11 ♀	3	++	+			
	4	+	+÷			
3 ÷ ♂	3	+	++?			
	4	?	?			5/9 42.
12 ♀	3	++	+++			
	4	+	+++			Photo No. 8.
13 ♂	3	++	++			
	4	++	+			
14 ♂	3	++	++			
	4	+	+			Photo No. 4.
15 ♀	3	+	+			
	4	+	+			Photo. No. 3.
9 ♂	3	++	++			12/9 42.
	4	+	+			
16 ♀	3	+	+			
	4	+	÷			Photo No. 10.
17 ÷ ♀	3	+ ?	÷			
	4	÷	÷			

(Cont.).

(Cont.).

Child.	Days after patch test was made	Vaccinated		Infected		
		Tin.	BCG	Tin.	BCG	
18÷ ♂	3	÷	÷			
	4	÷	÷			
19 ♂	3	++	+			
	4	++	+			
20 ♂	3	÷	÷			
	4	+	+			
21 ♂	3			++++	+	12/7 42.
	4			++++	+	Photo. No. 5.
22 ♀	3			++++	+	
	4			++++	+	Photo. No. 6.
23 ♂	3			++++	++	
	4			++++	++	Photo. No. 9.

The children marked ÷ showed a negative tuberculin reaction before the patch test.

been made too early in the (infectious) preallergic stage to have been positive. Roentgen examination 12/7 42 showed no definite pathological changes.

Patient No. 16. Girl b. 17/3 42. At the Infant's Home from 10/6 42. The father has had pulmonary tub. since 1935, but has been at work most of the time. Caverna since 1941. Child was BCG-vaccinated by a private physician 24/3 42. At this time the father did not live at home, but he was in contact with the child between 2 hospitalizations between 1/4—9/4 42. The vaccinating physician reports on 1/6 42: "typical vaccination Pirquet". 10/6 42 the child was admitted to the Home and 24/6 had a doubtful Hamburger reaction. On the same day a large local reaction after BCG is recorded, with a gomme 20 × 15 mm. On 3/7 42 the child had a strong positive Mantoux, and this remained constant although not quite so strong. Physical examination revealed "slightly unclear respiration over both tips", and her temperature was almost subfebrile at this time, around 38°. In the course of 5—6 weeks her temp. became normal and her general condition satisfactory, normal lung findings. Roentgen examinations 19/8 and 22/9 42 resulted in the following description from the Roentgen Department of the State Hospital: Possible small spotted shadow laterally and below the rt. hilus. Parenchyme congestion?

After the suspicious findings with the plaster reactions (Photo. 10) she was admitted to the Pediatric Dept. of the State Hospital. Here

she showed a doubtful Mantoux after $^1/_{10}$ mg. (10 × 10 mm. after 2 days, 6 × 6 mm. after 72 hours). The contents of the stomach gave no growth on Løwenstein, and roentgen examination showed the following: Below the rt. hilus a small-spotted and striped shadow in a limited area. This is presumably due to parenchyme congestion, the more so as this same shadow seems to have been present in pictures taken at the Infant's Home on $^{19}/_8$. D: Lung congestion on rt. side probable.

Patient No. 19. Boy b. $^{11}/_4$ 40. Stayed at Infant's Home I $^{30}/_4$ 41 to $^{12}/_7$ 41 and II $^{17}/_7$ 41 to Sept. 1942. The father was reported for pulmonary tub. 1935 but is now at work (roentgen shows calcification). The child was Pirquet ÷ $^{17}/_5$ 40 and $^{25}/_4$ 41. The boy was BCG-vaccinated $^{11}/_6$ 41 but was insufficiently isolated both before the vaccination (42 days) and after (1 month). On $^{27}/_7$ 41 Mantoux was + ÷ (10 × 12 mm. 48 hrs.), but has since been constantly and definitely positive. Unfortunately no roentgen examination has been made, as the child was discharged immediately after the patch tests.

In these patients the dominance of the tuberculin allergy is presumedly due to infection, which has been confirmed roentgenologically in some cases. We have also taken the practical consequence of these findings and placed these children in the isolation department for tuberculosis. In patient No. 19 the vaccination may have been performed in the pre-allergic phase, or the infection may have been contracted during the 5 days the child was at home between the 2 stays at the Infant's Home.

Among the infected 1 child (No. 23) shows a stronger reaction to the BCG-plaster than the other children (Photo. 9). It was found that he was BCG-vaccinated during a previous stay at the Infant's Home. After discharge he became infected and was re-admitted with a tuberculous infection (lung). The presence of specific BCG-antigen (?) after vaccination may possibly be the explanation of the relatively strong reaction to the BCG-plaster.

In patients Nos. 17 and 18 there was no reaction, probably because the tests were made such a short time after vaccination, 42 and 29 days respectively.

In patient No. 12 the reaction to the tuberculin plaster disappeared after 7 days, while the BCG-reaction persists for 10 days (Photo. 8). In patient No. 8 the BCG-reaction persists

Table 11. *Patch tests with killed human tubercle bacilli, killed BCG-bacilli (both 100 mg. per cc.) and Old-tuberculin.*

Child.	Days after patch test was made	Vaccinated			
		Tin.	BCG	TBC	
1 ♂	4	+	++	++	
	6	+	++	+	
9 ♂	4	+	++ (+)	+ (+)	
	6	÷	++	+	
27 ♂	4	+	++	++	$^{19}/_{4}$ 43.
	6	Pigment remains.			
28 ♂	4	+	+	++	
	6	÷	++	+	
29 ♀	4	÷	+ (+)	÷	
	6	÷	+ wk	÷	
3÷ ♂	3	÷	÷	÷	
	4	÷	÷	÷	
6 ♀	3	++	+++	+	
	4	+	++ (+)	++	Photo. No. 11.
8 ♀	3	++	+++	+++	
	4	++	+++	+++	Photo. No. 12.
17 ♀	3	+	++	++	$^{23}/_{4}$ 43.
	4	+	++	+++	
30 ♀	3	++	+	+÷	
	4	÷	+	÷	Photo. No. 13.
31 ♀	3	++	++	++	
	4	++	++ (+)	++	Photo. No. 14.
32 ♀	3	+	++	++	
	4	÷	+	+	

Infected.

16 ♀	4		++	+++	
	7		++	++	
24 ♀	4		++	+++	
	7		+	+ (+)	$^{12}/_{4}$ 43.
25 ♂	4		+	++	
	7		÷	÷	
26 ♂	4		++	+++	
	7		+	++	

for 17 days (Photo. 7) while the tuberculin reaction has disappeared.

The optimum time for observation of the reactions seems to be 4 to 6 days.

It would be of interest to see how virulent bacilli act in comparison in similar percutaneous reactions. This is shown in Table 11 where, in addition to tuberculin plaster and BCG-plaster, a plaster with killed (60°, $^1/_2$ hr.) virulent human bacilli (strain H—37) in the same concentration as BCG (100 mg. per cc.) is used. The technique is otherwise the same as described above with removal of the plasters after 2 days.

The children are partly the same as used in the previous tests (cf. pat. Nos.).

This table shows that the BCG-reaction in the vaccinated is stronger than the tuberculin reaction. In some cases (1, 6?, 9, 28, 29, 30, 31?) the skin reactions to BCG are stronger than the reactions to killed virulent bacilli.

In the infected individuals the reaction to the plaster with virulent bacilli is the strongest.

With these reactions as a starting point it should perhaps be possible to work out a practical method of distinguishing infection allergy and vaccination allergy. This could be done most simply by preparing plasters similar to Astra's tuberculin plaster, but with 3 patches instead of 2 as in the following sketch:

In the center a control plaster with broth and on either side plaster with Old-tuberculin and *killed* BCG respectively.

The concentration of the BCG must be experimentally determined; 1—10 mg. BCG per plaster surface is probably necessary. Difficulties of communication, lack of materials etc. have prevented further experimentation in this field for the present.

Summary.

Percutaneous tests—patch tests—with killed BCG give stronger reactions in vaccinated children than percutaneous tests with Old-tuberculin, or equally strong reactions.

In infected children the percutaneous reactions with Old-tuberculin are stronger.

PHOTOS 3 AND 4.

Patch tests in BCG-vaccinated. Reactions with OT and BCG relatively equal.

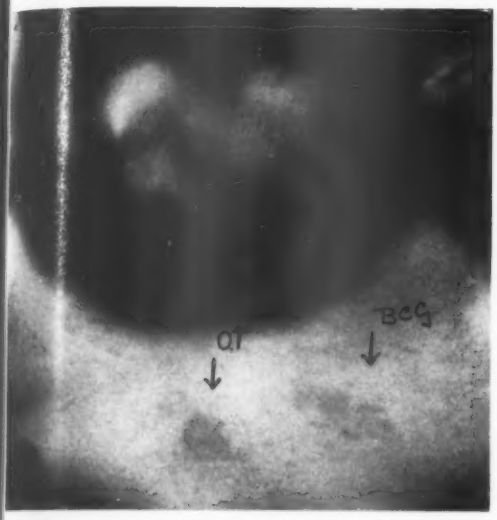

Photo 3.

Pat. 15, Table 10. L. O. b. $^{1}/_{10}$ 41.
BCG I $^{13}/_{10}$ 41 0.10 mg.
" II $^{12}/_{11}$ 41 " " (+)
" III $^{20}/_{1}$ 42 " " (+)
" IV $^{27}/_{5}$ 42 0.05 " (+)
Mantoux ÷ $^{26}/_{10}$41, $^{9}/_{1}$, $^{6}/_{3}$ 42.
Photo $^{15}/_{9}$ 42 after patch test $^{12}/_{9}$ 42.

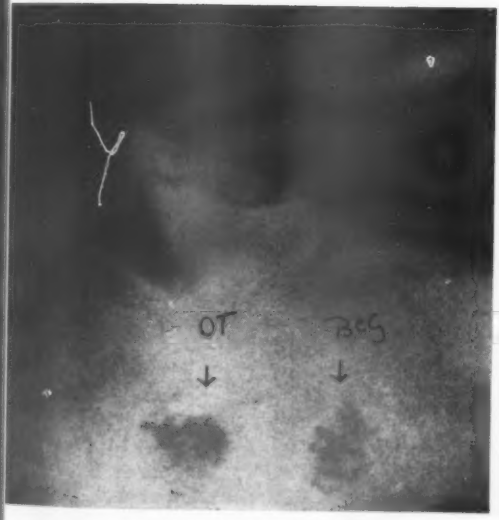

Photo 4.

Pat. 14, Table 10. E. T. b. $^{11}/_{6}$ 40.
BCG I $^{12}/_{6}$ 40 Rosenthal
" II $^{24}/_{9}$ 41 0.05 mg. (+)
Mant. ÷ $^{9}/_{9}$ 41, H+ $^{30}/_{9}$ 41.
Photo $^{15}/_{9}$ 42 after patch test $^{12}/_{9}$ 42.

PHOTOS 5 AND 6.

Patch tests in infected children. Photos taken $^{15}/_{9}$ 42 after patch tests $^{12}/_{9}$ 42. OT stronger in both.

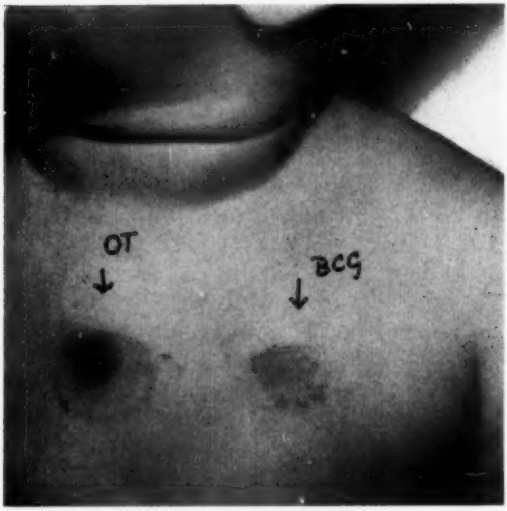

Photo 5.

Pat. 21, Table 10. R. B. b. $^{9}/_{3}$ 41. D: Infiltratio pulm.

Photo 6.

Pat. 22, Table 10. H. S. b. $^{25}/_{11}$ 40. D: Infiltratio pulm.

PHOTOS 7 AND 8.

Duration of the BCG-patch test reaction.

Photo 7.

Pat. 8, Table 10. J. A. b. $^{2}/_{11}$ 40.
BCG I $^{23}/_{9}$ 41 0.05 mg. (+)
" II $^{13}/_{1}$ 41 " " (+)
" III $^{5}/_{11}$ 41 0.10 mg. (+)
M ÷ $^{10}/_{10}$ 41
M ÷ $^{27}/_{10}$ 41
M+, H+ $^{29}/_{11}$ 41
Photo taken $^{15}/_{9}$ 42 — 17 days after patch test with 100 mg. killed BCG ($^{29}/_{8}$ 42) still shows pronounced reaction here, while the reaction at OT has practically disappeared.

Photo 8.

Pat. 12, Table 10. V. A. b. $^{11}/_{5}$ 41.
BCG I $^{4}/_{11}$ 41 0.10 mg.
M+ $^{28}/_{11}$ 41, H+ $^{9}/_{1}$, $^{18}/_{2}$ 42.
Photo taken $^{15}/_{9}$ 42 after patch test with 100 mg. killed BCG $^{5}/_{9}$ 42 shows persistent visible reaction to BCG 10 days later while reaction at OT has disappeared ($^{13}/_{9}$ 42).

PHOTO 9.

Patch test reaction in vaccinated children who were subsequently infected,

Photo 9.

Pat. 23. Table 10. A. A. b. $^{11}/_{6}$ 41. BCG $^{21}/_{7}$ 41 0.05 mg. (+), M÷ $^{5}/_{9}$ 41. Very strong BCG reaction in comparison to the other infected children. Is this due to the specific BCG antigen in connection with the vaccination?

PHOTO 10.

Patch test in vaccinated and infected.

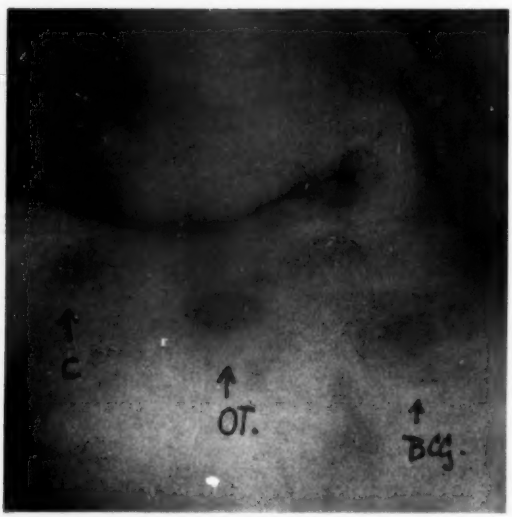

Photo 10.

Pat. 16, Table 10. U. Ø. b. $^{17}/_{3}$ 42. BCG $^{24}/_{3}$ 42. H+÷ $^{24}/_{6}$ 42. M+ $^{3}/_{7}$ 42. Photo taken $^{15}/_{9}$ 42 after patch test $^{12}/_{9}$ shows stronger reaction at OT than at BCG. $^{16}/_{9}$ OT is pos, BCG neg. This leads to re-examination of case history, which reveals possibility of virulent infection $^{1}/_{4}$—$^{9}/_{4}$ 42.

PHOTOS 11, 12, 13, 14.

Plaster reactions with killed human tubercle bacilli, Old-tuberculin and killed BCG-bacilli in vaccinated children. All photos taken $^{27}/_{4}$ 43 after plaster reactions $^{23}/_{4}$; the reactions are thus 4 days old.

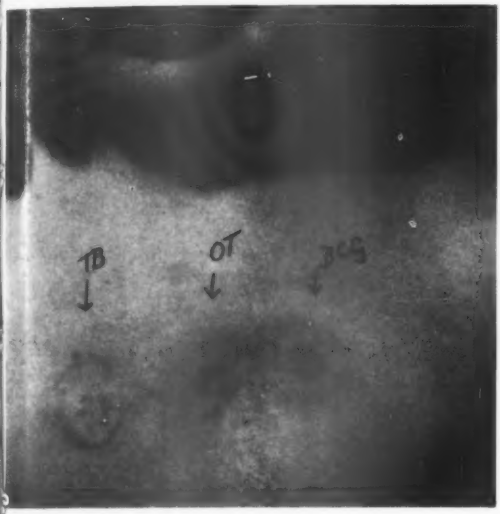

Photo 11.

Pat. 6, Table 11. S. M. b. $^{22}/_{10}$ 39.
BCG I $^{28}/_{10}$ 39 0.10 mg.
" II $^{8}/_{3}$ 40 " "
" III $^{5}/_{5}$ 41 0.5 " +
M ÷ $^{15}/_{12}$ 39, $^{17}/_{1}$ 40, $^{18}/_{6}$ 40, $^{12}/_{7}$ 40.
M + $^{23}/_{8}$ 40, $^{10}/_{10}$ 40,
M ÷ $^{19}/_{4}$ 41. M + $^{28}/_{5}$, $^{27}/_{6}$ 41.
Tuberculin reaction weaker than the bacilli reactions, which are more small-papular; possible somewhat stronger reaction to BCG than to TB.

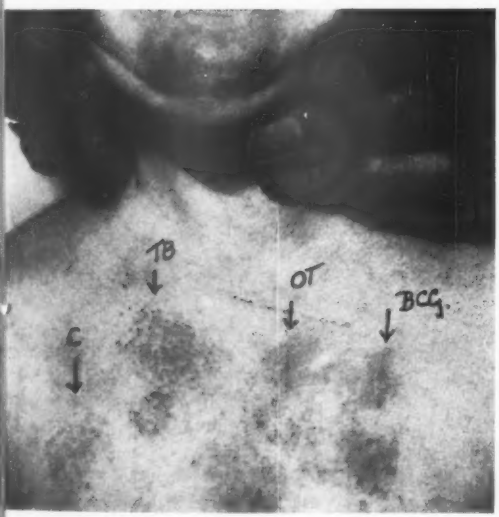

Photo 12.

Pat. 8, Table 11. J. A. b. $^{2}/_{11}$ 40.
BCG I $^{23}/_{9}$ 41 0.05 mg. +
" II $^{13}/_{10}$ 41 " " +
" III $^{5}/_{11}$ 41 0.10 " +
M ÷ $^{10}/_{10}$, $^{27}/_{10}$, $^{14}/_{11}$ 41.
H ++ $^{29}/_{11}$ 41, $^{9}/_{1}$, $^{17}/_{4}$ 42.

PHOTOS 13 AND 14.

Photo 13.

Pat. 30, Table 11. T. R. b. [illegible]/9 42.
RCG 16/10 42 0.10 mg.
M ÷ 6/11, 5/12.
M + 18/12 42, 15/1, 6/4 43.
BCG-reaction still persists as well as weak OT. TB-reaction has disappeared.

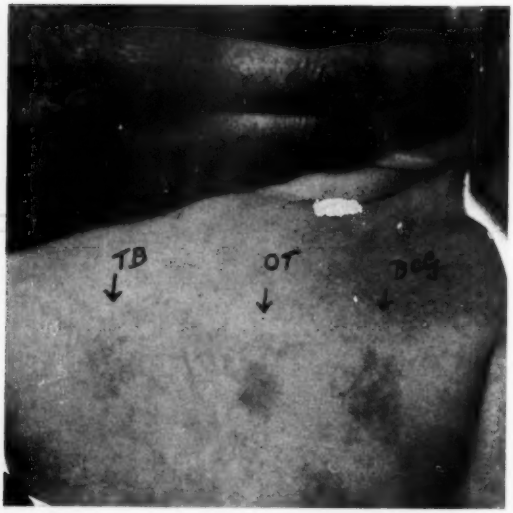

Photo 14.

Pat. 31, Table 11. R. S. b. 12/10 42.
BCG 21/12 42 0.05 mg.
M ÷ 6/1 43.
P + (?) 30/1 43. M + 1/9 43.
BCG-reaction stronger than TB.

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